

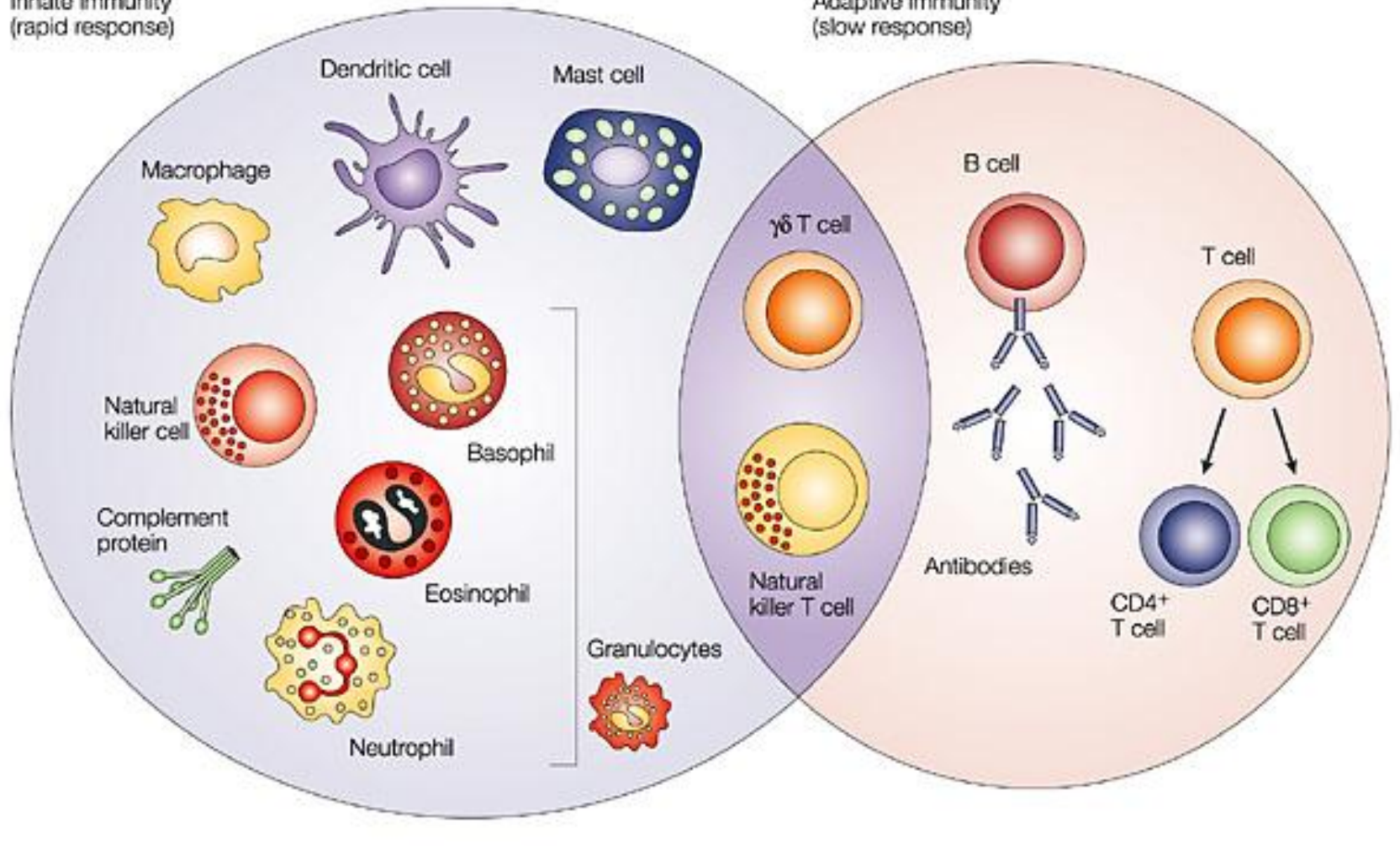
Guillermo Terán-Ángel
IDIC-ULA

**Fisiología de la respuesta
inmunitaria innata**

Ubicándonos

Innate immunity
(rapid response)

Adaptive immunity
(slow response)

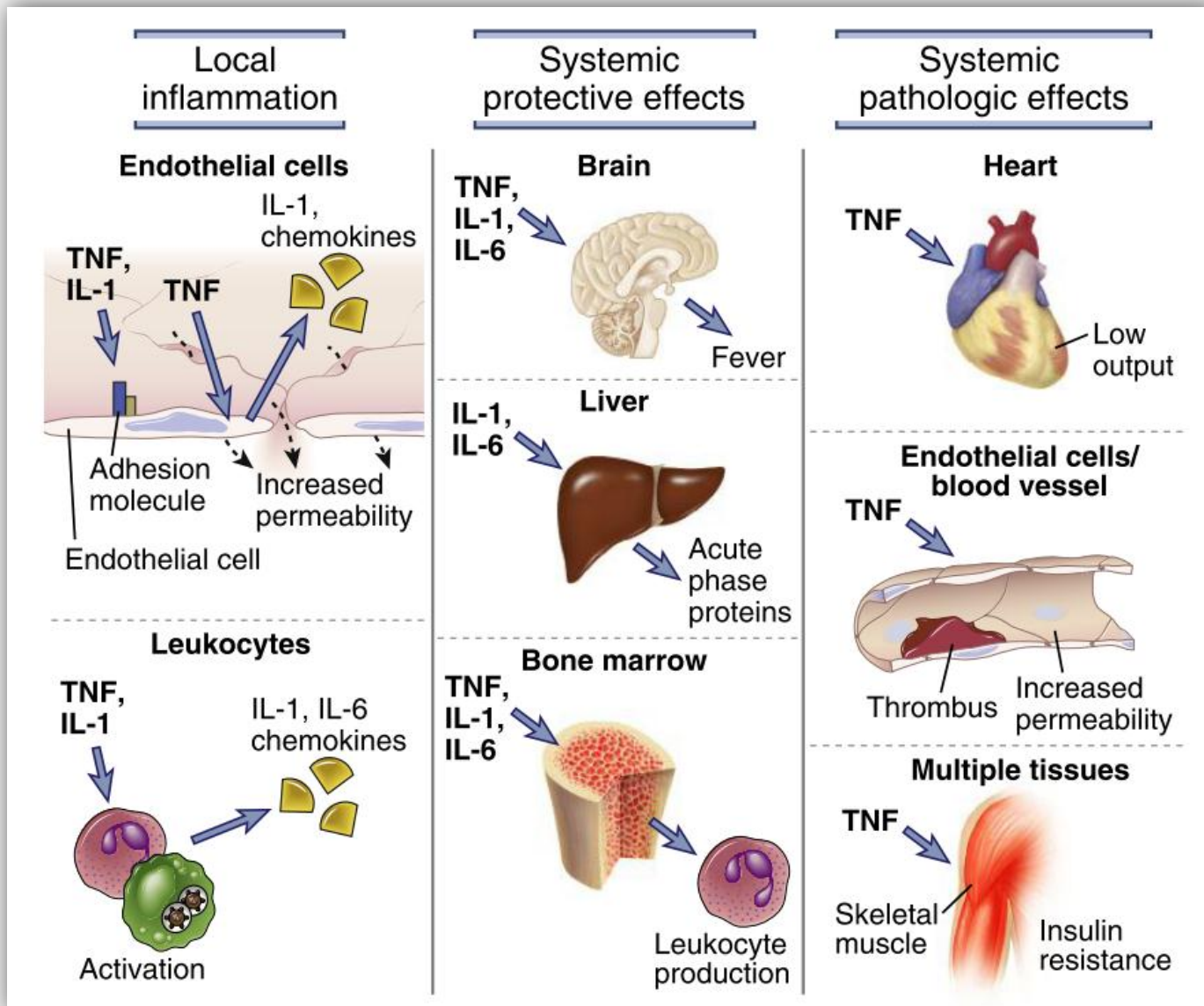


No sólo leucocitos

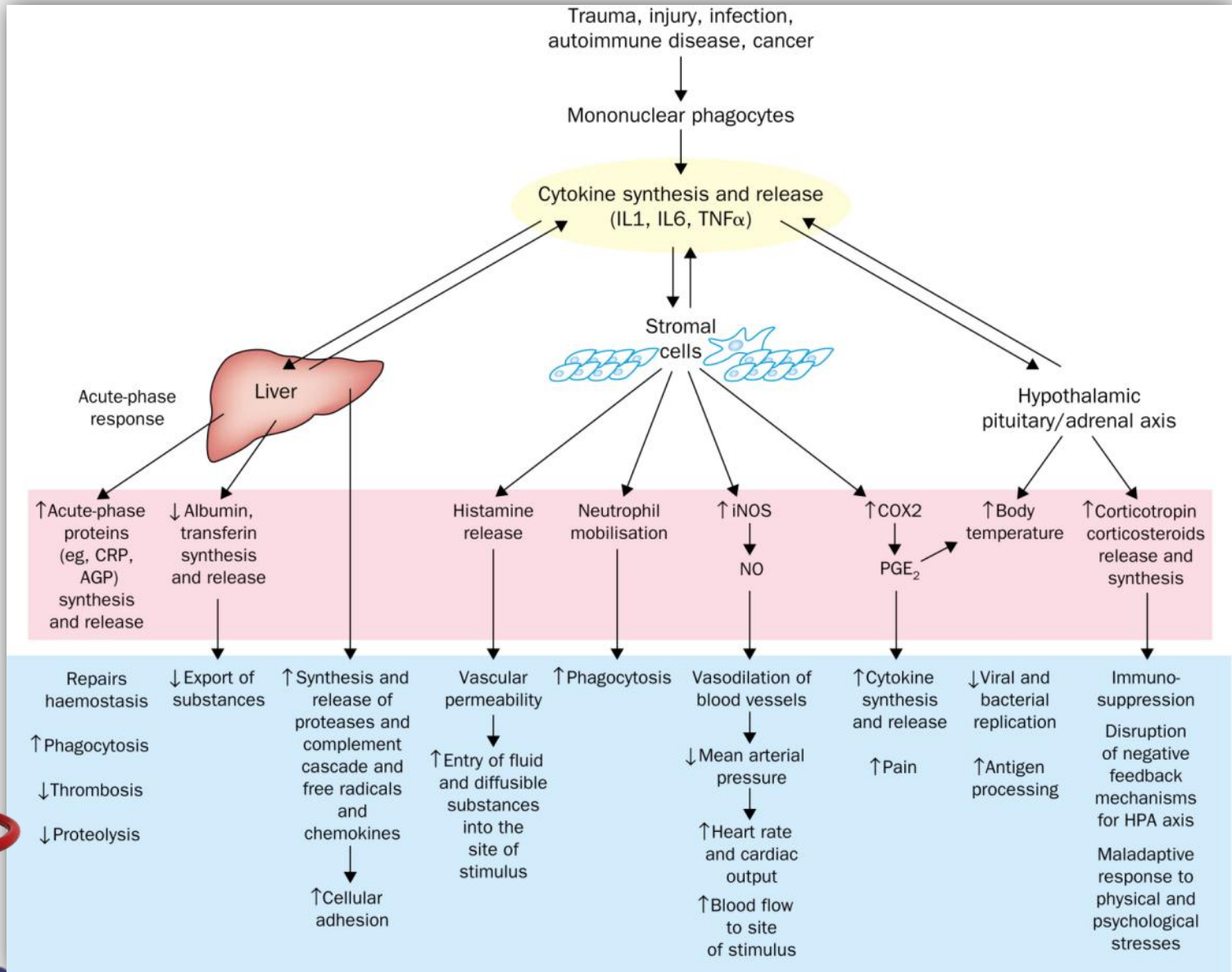


	Skin	Gut	Lungs	Eyes/nose/oral cavity
Mechanical	Epithelial cells joined by tight junctions			
	Longitudinal flow of air or fluid		Movement of mucus by cilia	Tears Nasal cilia
Chemical	Fatty acids	Low pH	Pulmonary surfactant	Enzymes in tears and saliva (lysozyme)
		Enzymes (pepsin)		
	β -defensins Lamellar bodies Cathelicidin	α -defensins (cryptdins) RegIII (lecticidins) Cathelicidin	α -defensins Cathelicidin	Histatins β -defensins
Microbiological	Normal microbiota			

Respuesta aguda



Respuesta aguda



Proteínas de fase aguda

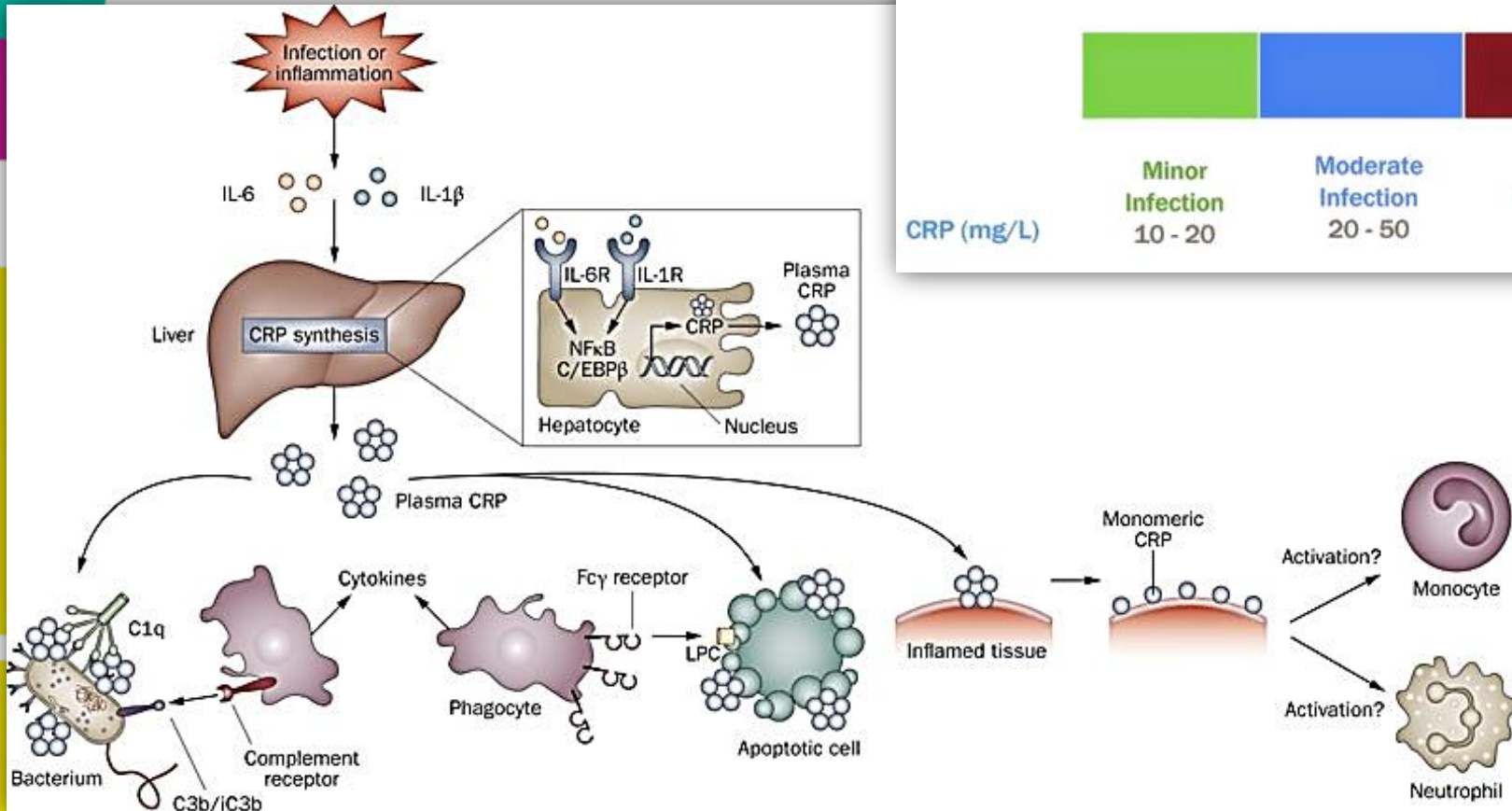
Proteína	Función en el sistema inmunológico
Proteína C reactiva	<ul style="list-style-type: none">• Oponina que actúa sobre microbios
Amiloide sérico componente P	<ul style="list-style-type: none">• Oponina
Amiloide A sérico	<ul style="list-style-type: none">• Reclutamiento de las células inmunitarias al sitio de inflamación• Inducción de enzimas que degradan la matriz extracelular
Factores del complemento	<ul style="list-style-type: none">• Oponización, lisis y aglutinación de las células diana. Quimiotaxis
Lectina de unión a manosa	<ul style="list-style-type: none">• Vía de la lectina en la activación del complemento
Fibrinógeno, protrombina, factor VIII, Factor de von Willebrand	<ul style="list-style-type: none">• Factores de coagulación, atrapamiento de microorganismos invasores en coágulos sanguíneos. Algunos provocan quimiotaxis
Plasminógeno	<ul style="list-style-type: none">• Degradación de los coágulos sanguíneos
Alfa-2-Macroglobulina	<ul style="list-style-type: none">• Inhibidor de la coagulación por medio de la inhibición de la trombina.• Inhibidor de la fibrinólisis por medio de la inhibición de la plasmina
Ferritina	<ul style="list-style-type: none">• Fijadora de hierro, limita el acceso microbiano al hierro necesario para su metabolismo
Hepcidina	<ul style="list-style-type: none">• Estimula la internalización de la ferroportina, previniendo la liberación del hierro fijado por la ferritina dentro de los enterocitos y macrófagos
Ceruloplasmina	<ul style="list-style-type: none">• Oxida al hierro, facilitando su fijación por la ferritina, inhibiendo así el acceso microbiano al hierro.
Haptoglobina	<ul style="list-style-type: none">• Fija a la hemoglobina, inhibiendo el acceso microbiano al hierro
Orosomucoide (glicoproteína ácida alfa-1, AGP)	<ul style="list-style-type: none">• Transportadora de esteroides
Alfa 1-antitripsina	<ul style="list-style-type: none">• Serpina, regula a la baja la inflamación
Alfa 1-antiquimotripsina	<ul style="list-style-type: none">• Serpina, regula a la baja la inflamación

PCR, no PCR, es decir: RCP, no RCP

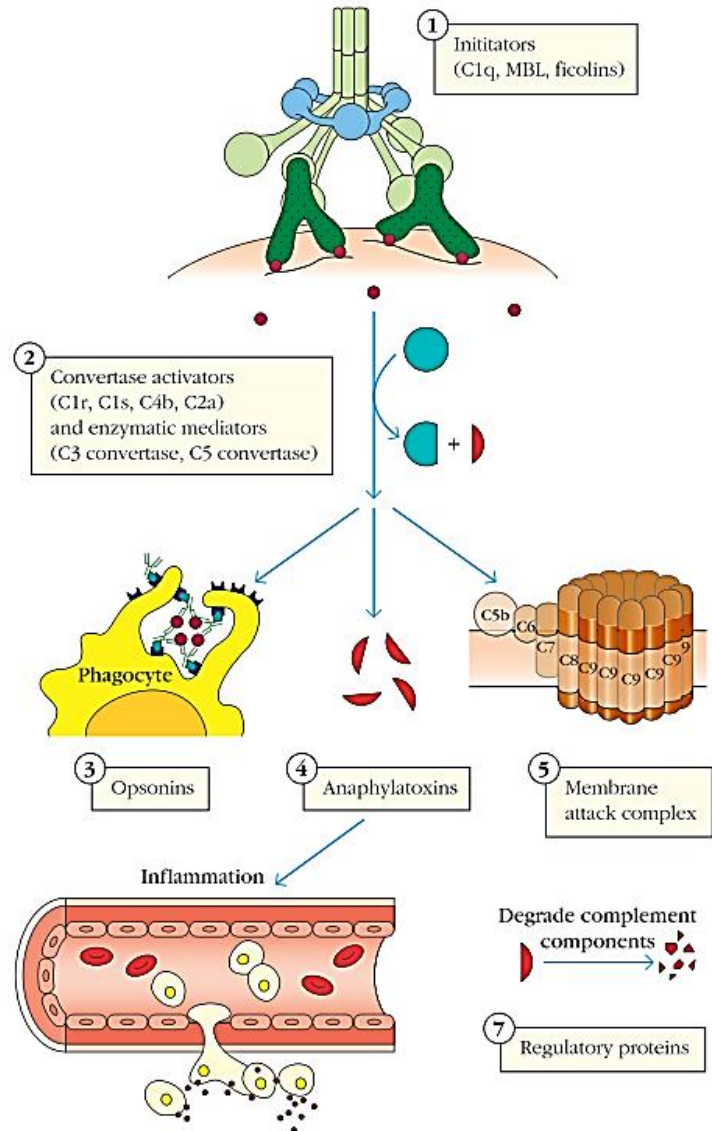


	Healthy	Local Infection	Systemic Infection	Severe Sepsis	Septic Shock
PCT (ng/ml)	0 - 0.1	0.1 - 0.5	0.5 - 2.0	2.0 - 10	> 10

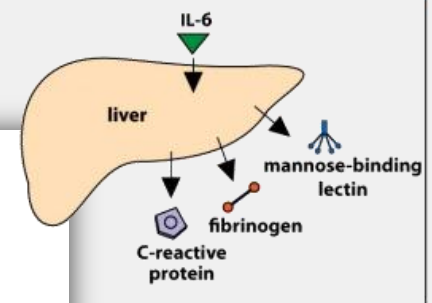
	Minor Infection	Moderate Infection	Severe Infection
CRP (mg/L)	10 - 20	20 - 50	> 50



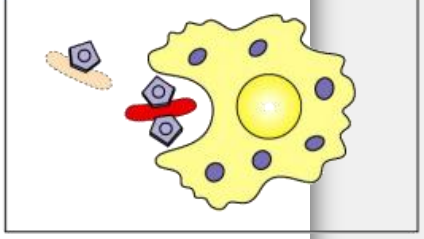
El complemento



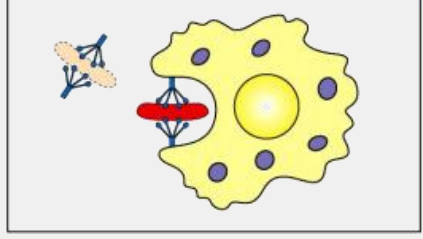
Bacteria induce macrophages to produce IL-6, which acts on hepatocytes to induce synthesis of acute-phase proteins



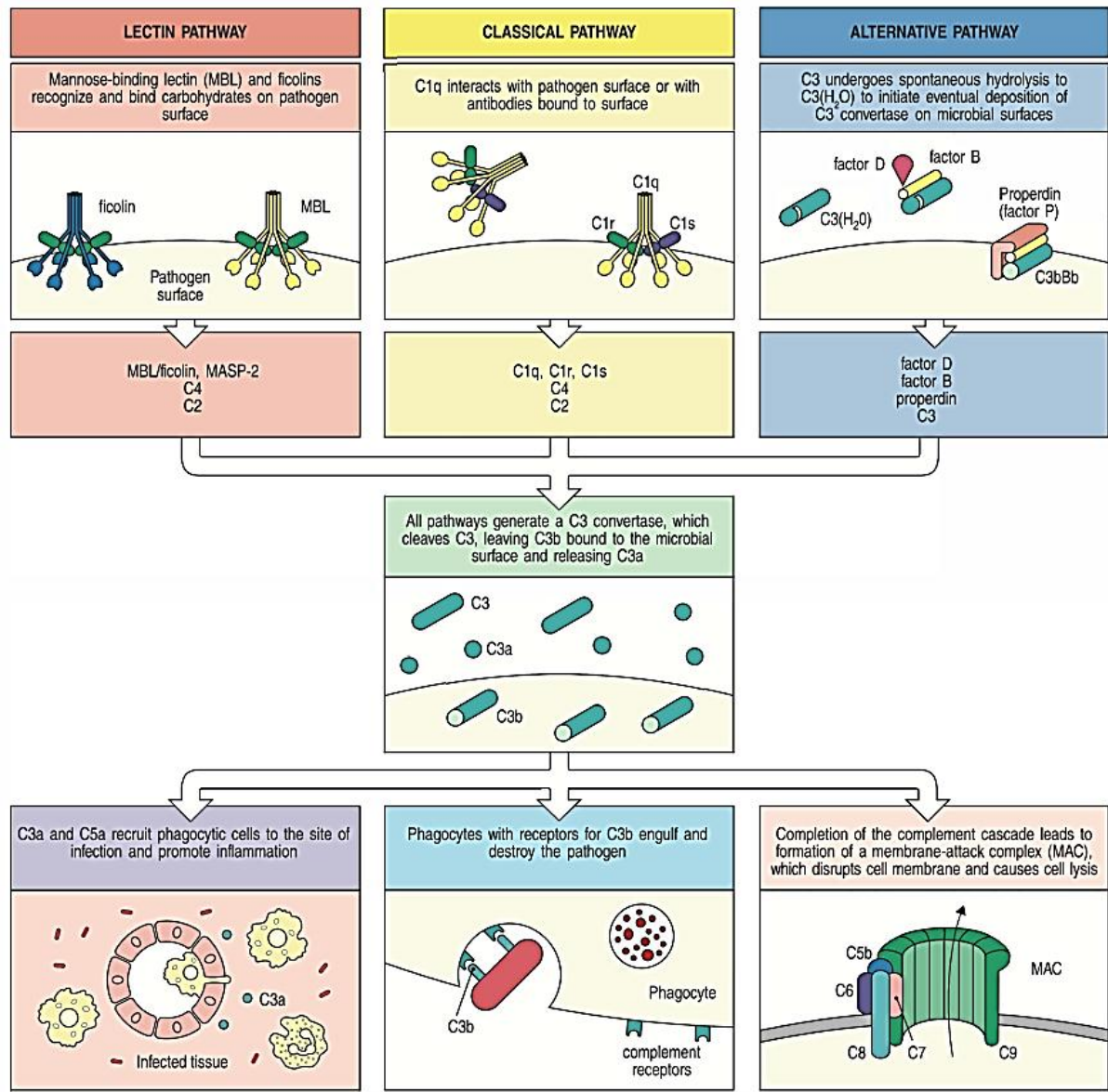
C-reactive protein binds phosphocholine on bacterial surfaces, acting as an opsonin and as a complement activator



Mannose-binding lectin binds to carbohydrates on bacterial surfaces, acting as an opsonin and as a complement activator

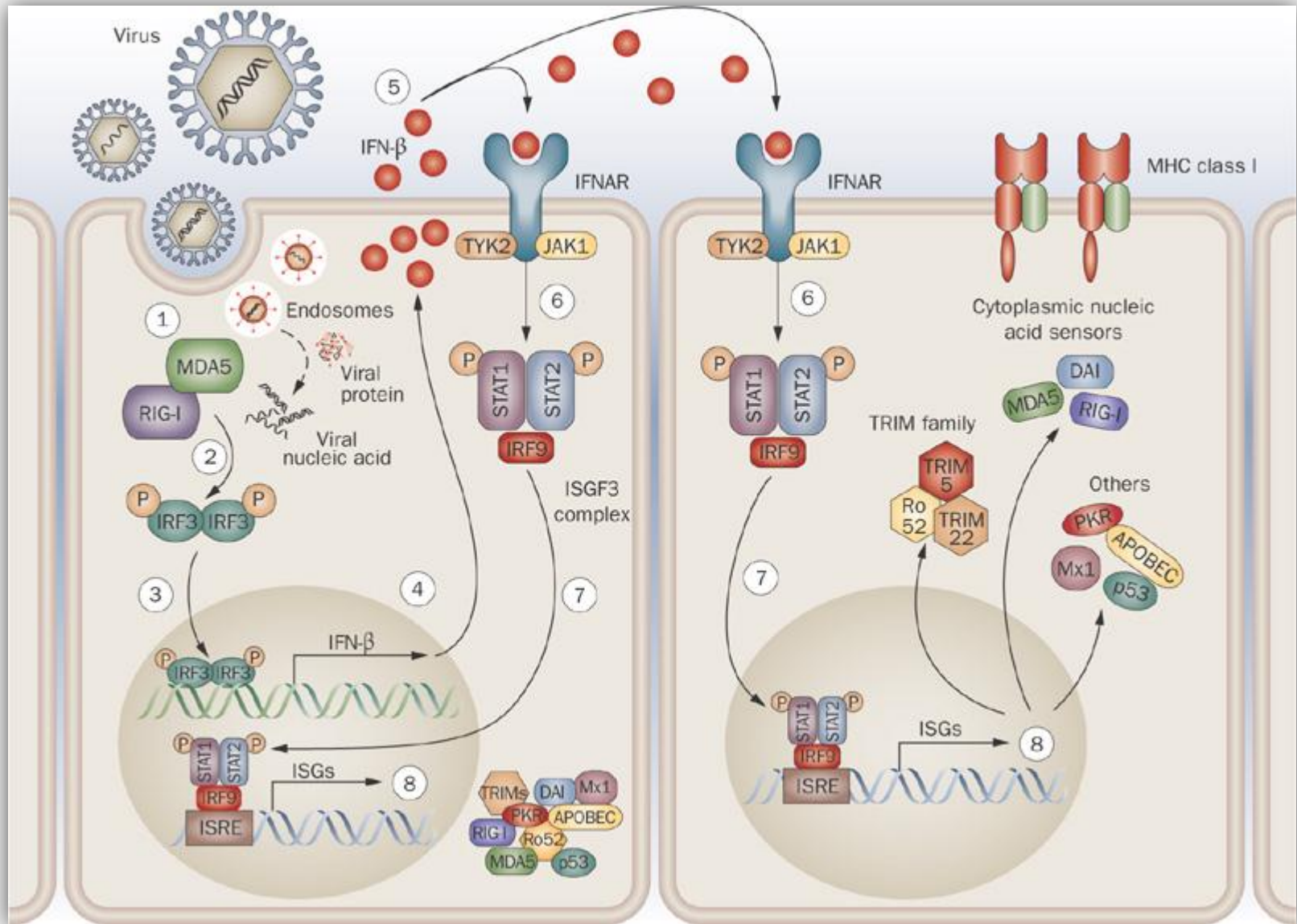


El complemento



Functional protein classes in the complement system	
Binding to antigen:antibody complexes and pathogen surfaces	C1q
Binding to carbohydrate structures such as mannose or GlcNAc on microbial surfaces	MBL Ficolins C1q Properdin (factor P)
Activating enzymes	C1r C1s C2a Bb D MASP-2
Membrane-binding proteins and opsonins	C4b C3b
Peptide mediators of inflammation	C5a C3a C4a
Membrane-attack proteins	C5b C6 C7 C8 C9
Complement receptors	CR1 CR2 CR3 CR4 CRIg
Complement-regulatory proteins	C1INH C4BP CR1 MCP DAF H I P CD59

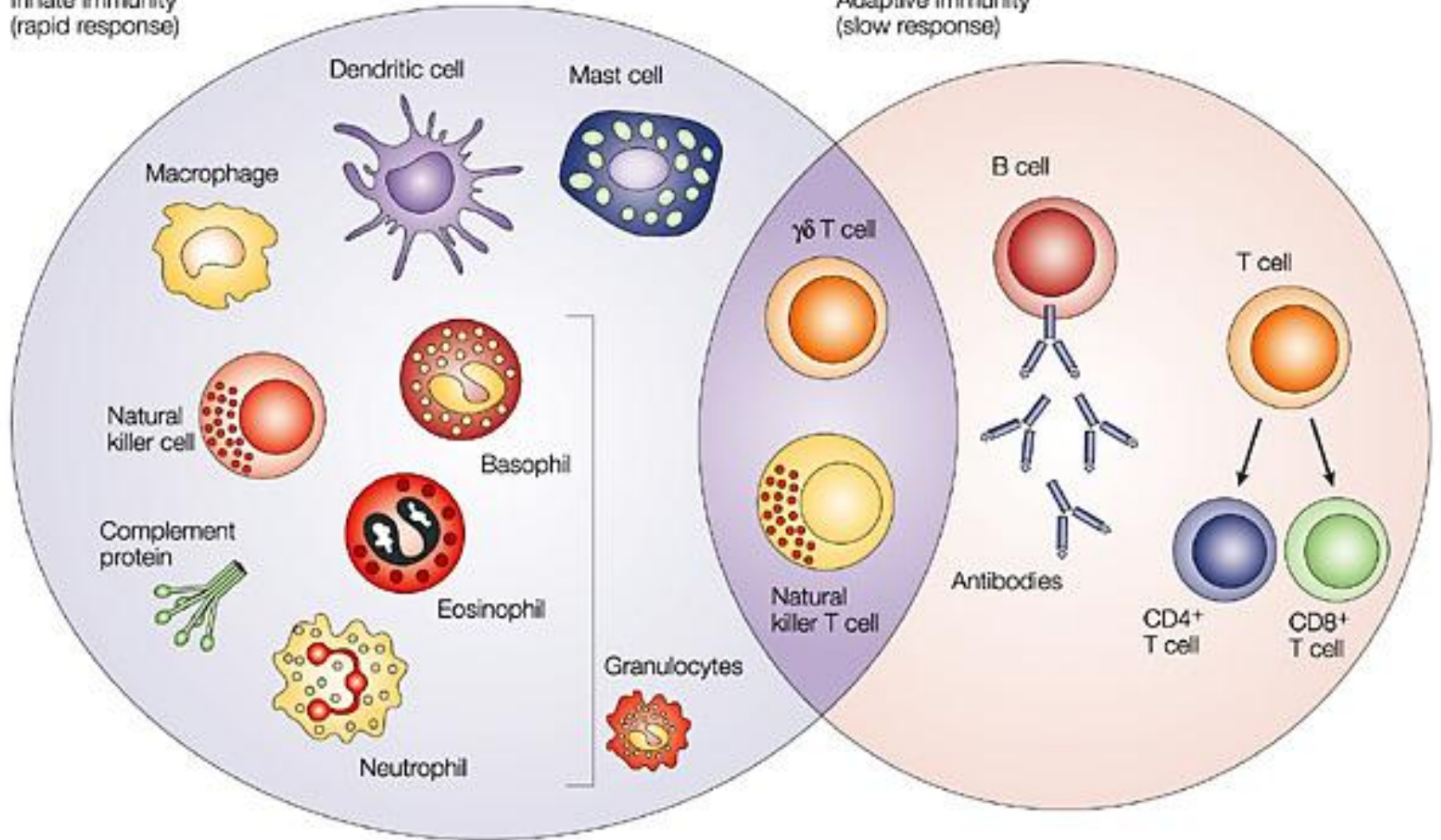
También los interferones



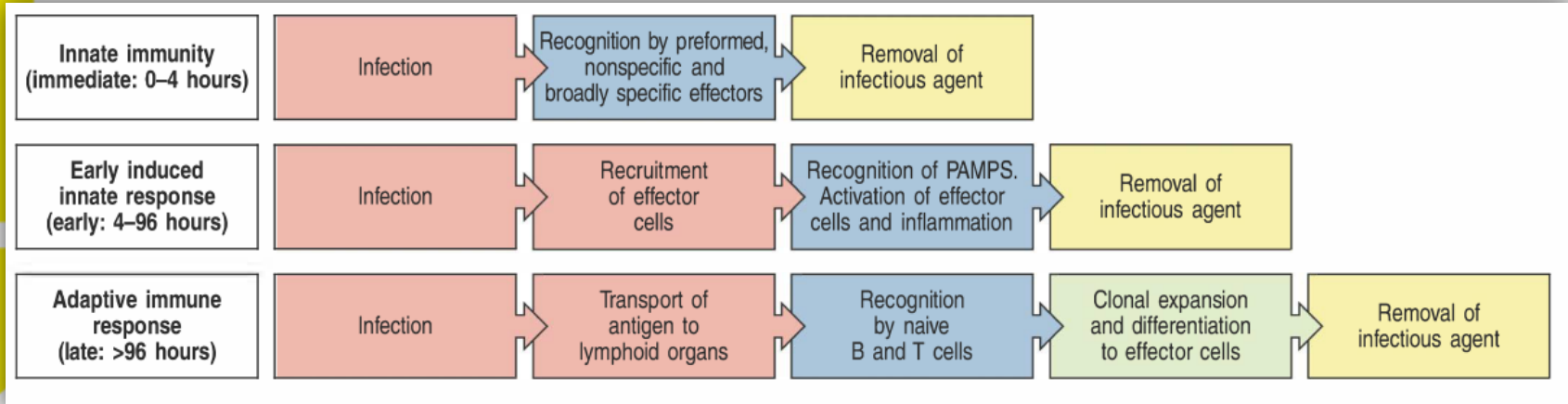
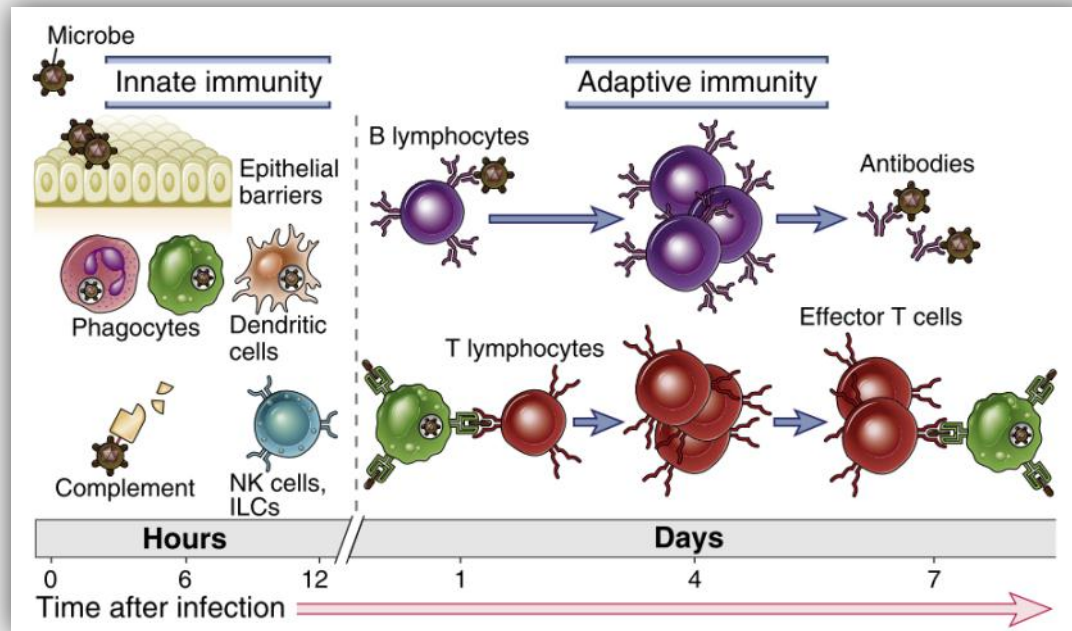
Veamos de nuevo

Innate immunity
(rapid response)

Adaptive immunity
(slow response)



Características de la respuesta innata



Características de la respuesta innata

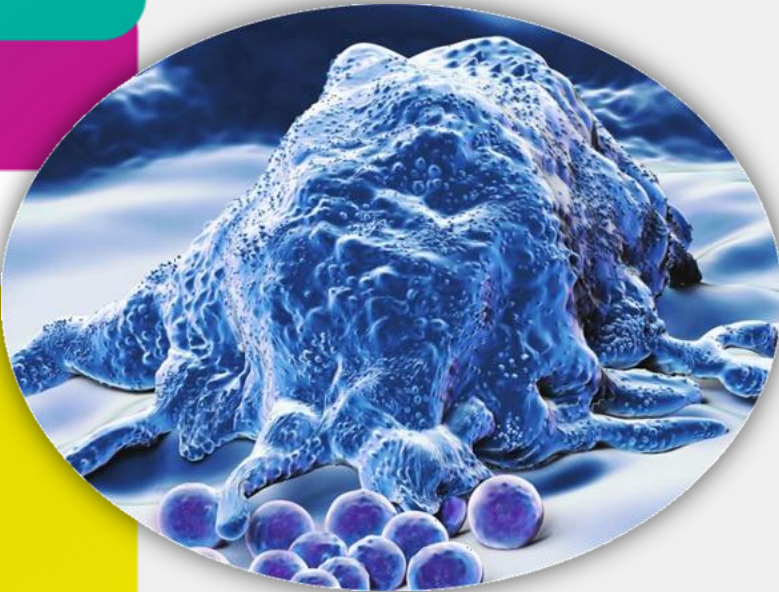
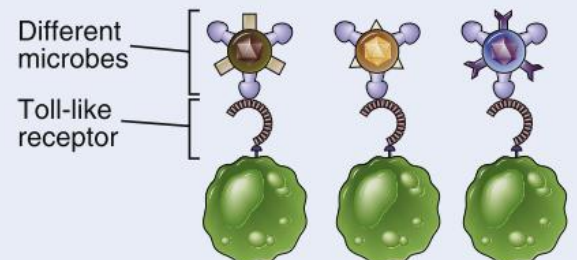
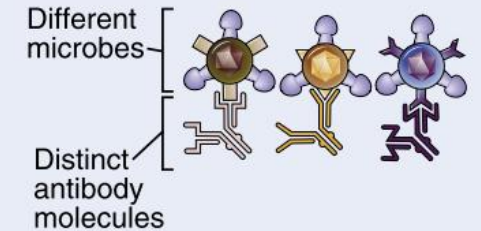
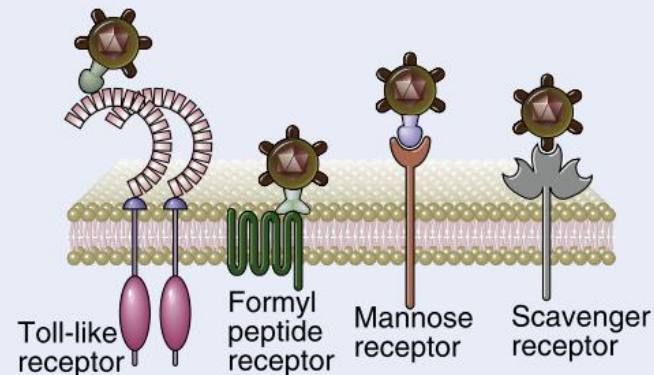
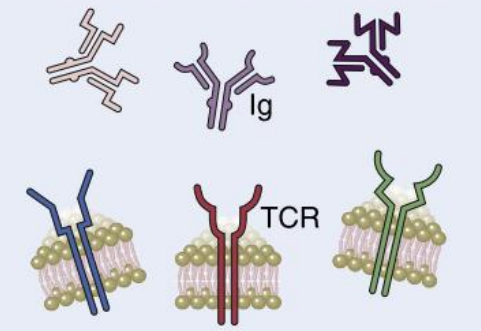


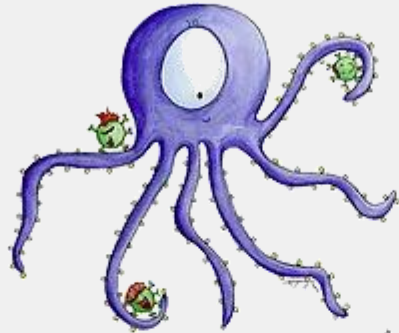
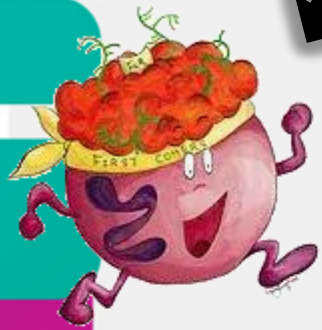
TABLE 1-2 Features of Innate and Adaptive Immunity

	Innate	Adaptive
Characteristics		
Specificity	For molecules shared by groups of related microbes and molecules produced by damaged host cells	For microbial and non-microbial antigens
Diversity	Limited; germline encoded	Very large; receptors are produced by somatic recombination of gene segments
Memory	None	Yes
Nonreactivity to self	Yes	Yes
Components		
Cellular and chemical barriers	Skin, mucosal epithelia; antimicrobial molecules	Lymphocytes in epithelia; antibodies secreted at epithelial surfaces
Blood proteins	Complement, others	Antibodies
Cells	Phagocytes (macrophages, neutrophils), natural killer cells, innate lymphoid cells	Lymphocytes

Diferencia crucial

TABLE 4-1 Specificity of Innate and Adaptive Immunity		
	Innate Immunity	Adaptive Immunity
Specificity	For structures shared by classes of microbes (pathogen-associated molecular patterns)	For structural detail of microbial molecules (antigens); may recognize nonmicrobial antigens
	<p>Different microbes</p> <p>Toll-like receptor</p> 	<p>Different microbes</p> <p>Distinct antibody molecules</p> 
Receptors	Encoded in germline; limited diversity (pattern recognition receptors)	Encoded by genes produced by somatic recombination of gene segments; greater diversity
	 <p>Toll-like receptor</p> <p>Formyl peptide receptor</p> <p>Mannose receptor</p> <p>Scavenger receptor</p>	 <p>Ig</p> <p>TCR</p>
Distribution of receptors	Nonclonal: identical receptors on all cells of the same lineage	Clonal: clones of lymphocytes with distinct specificities express different receptors
Discrimination of self and non-self	Yes; healthy host cells are not recognized or they may express molecules that prevent innate immune reactions	Yes; based on elimination or inactivation of self-reactive lymphocytes; may be imperfect (giving rise to autoimmunity)

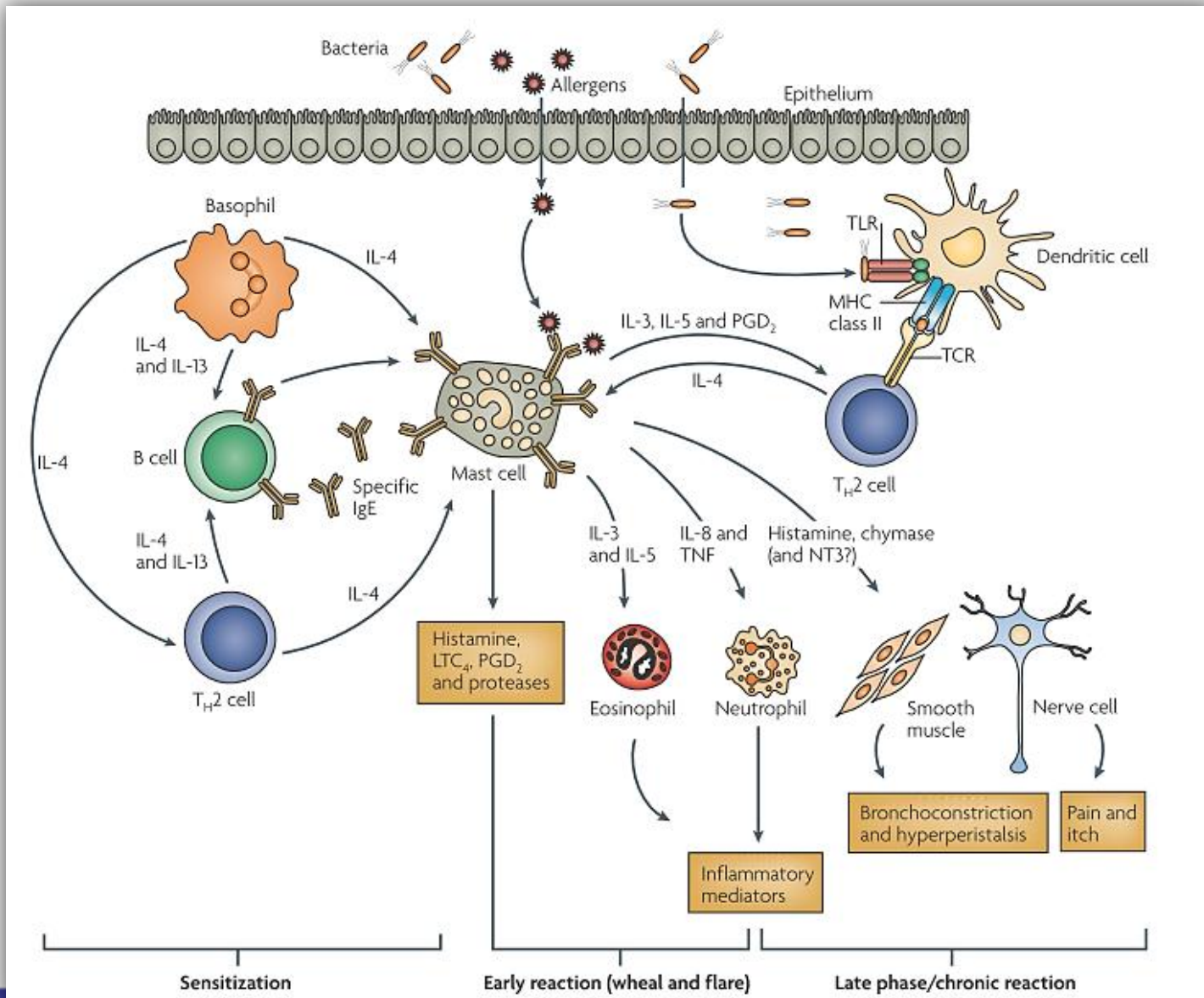
Conozcamos a los actores



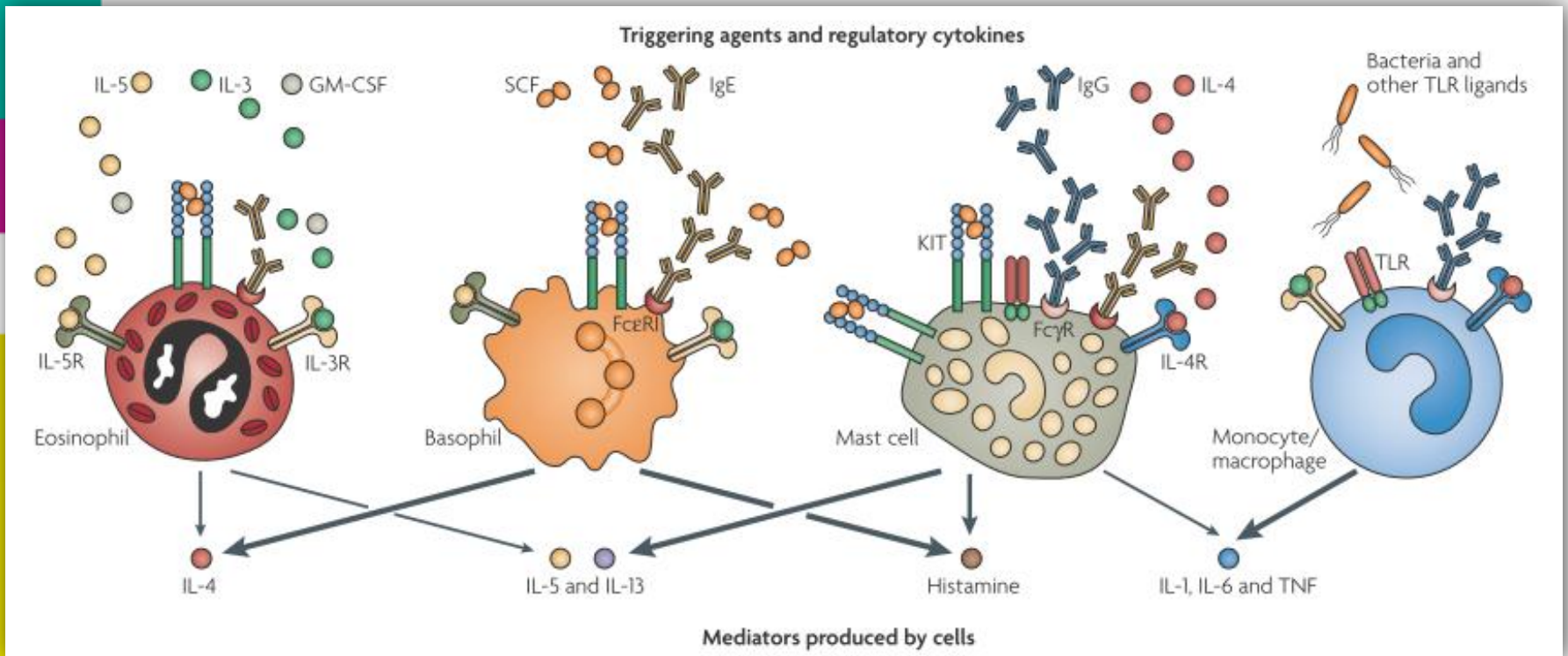
Eosinófilos, basófilos, y mastocitos



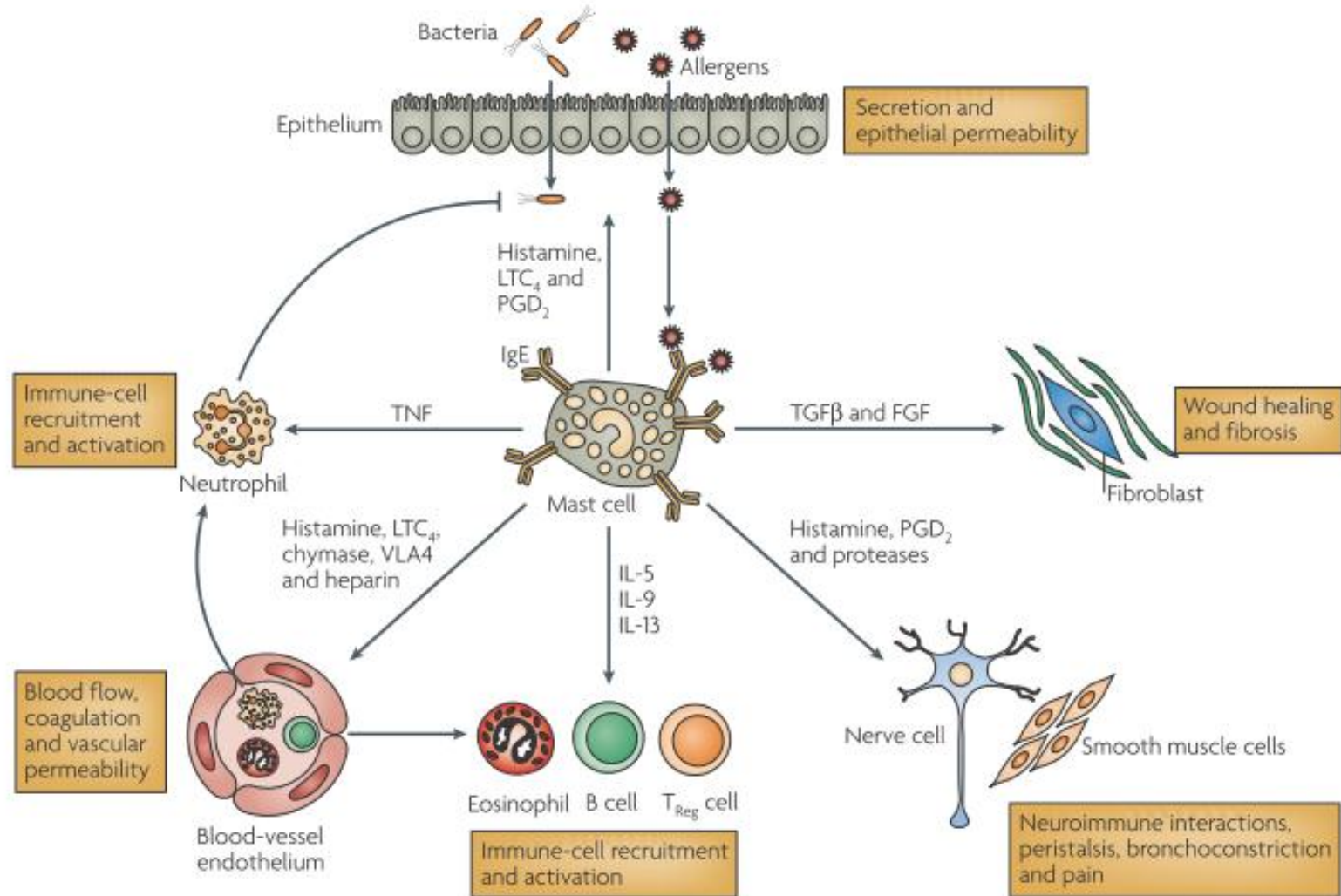
En el frente de las batallas alérgicas



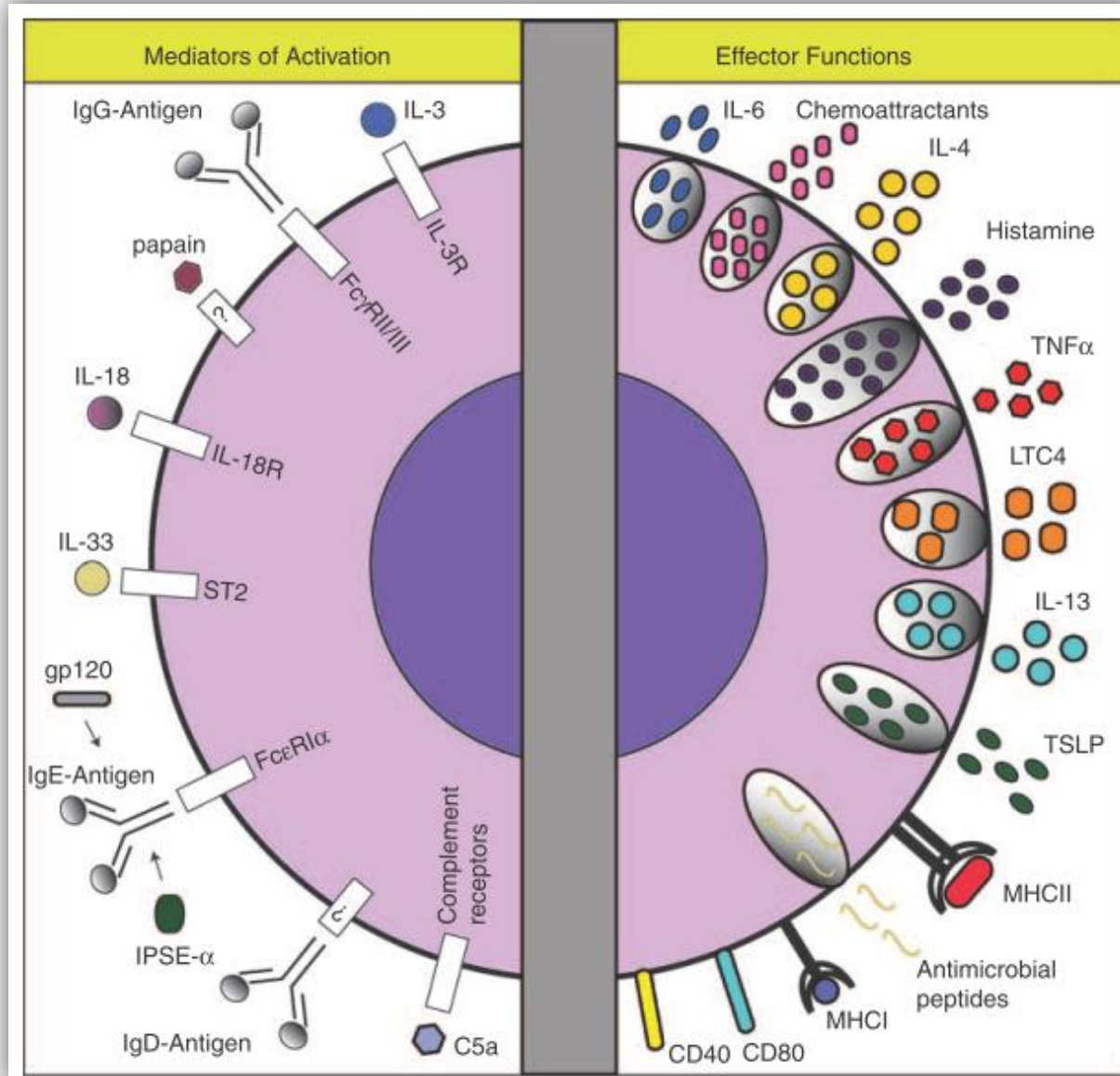
Características



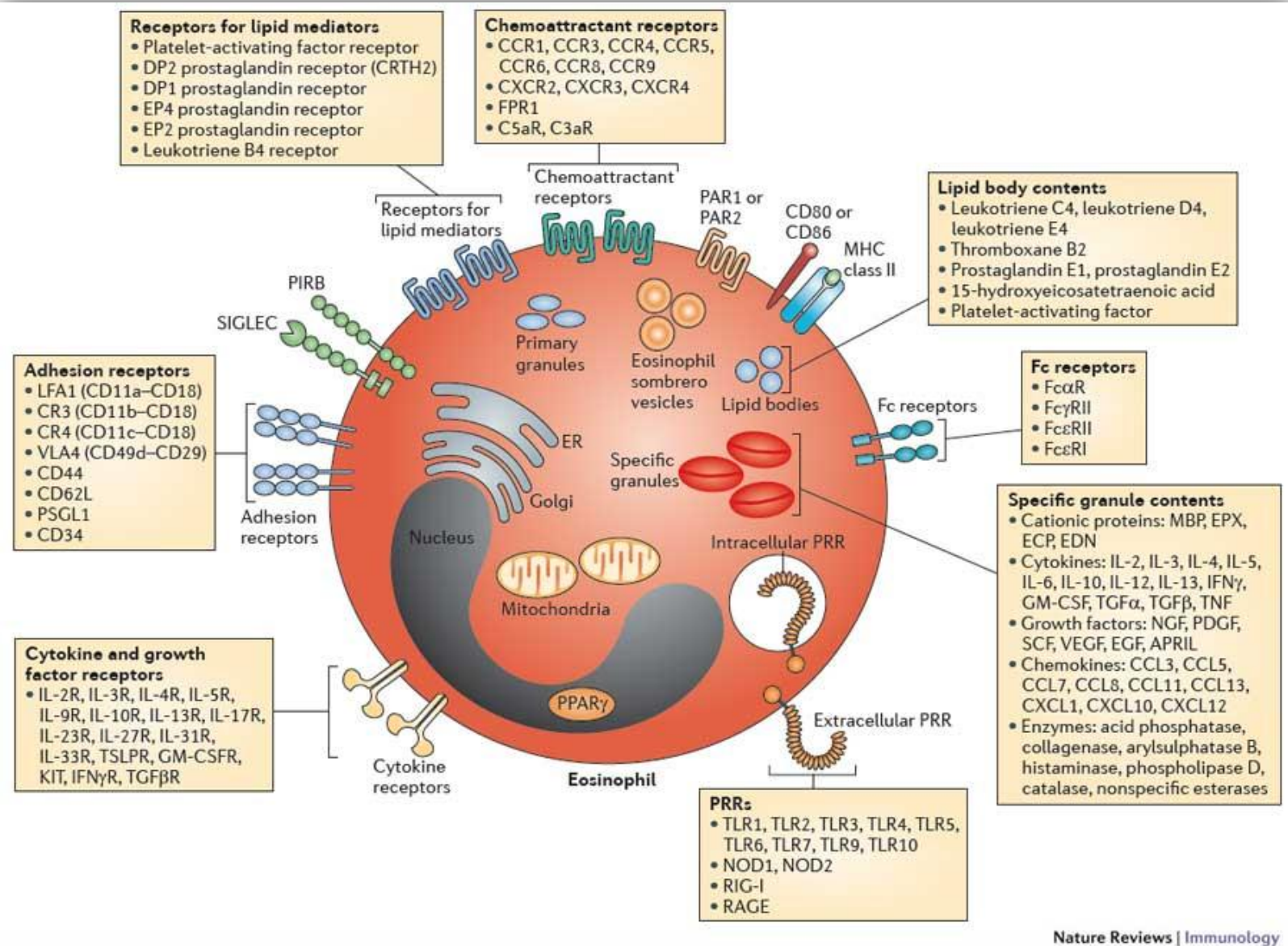
El mastocito, el incomprendido



El basófilo, el TH2

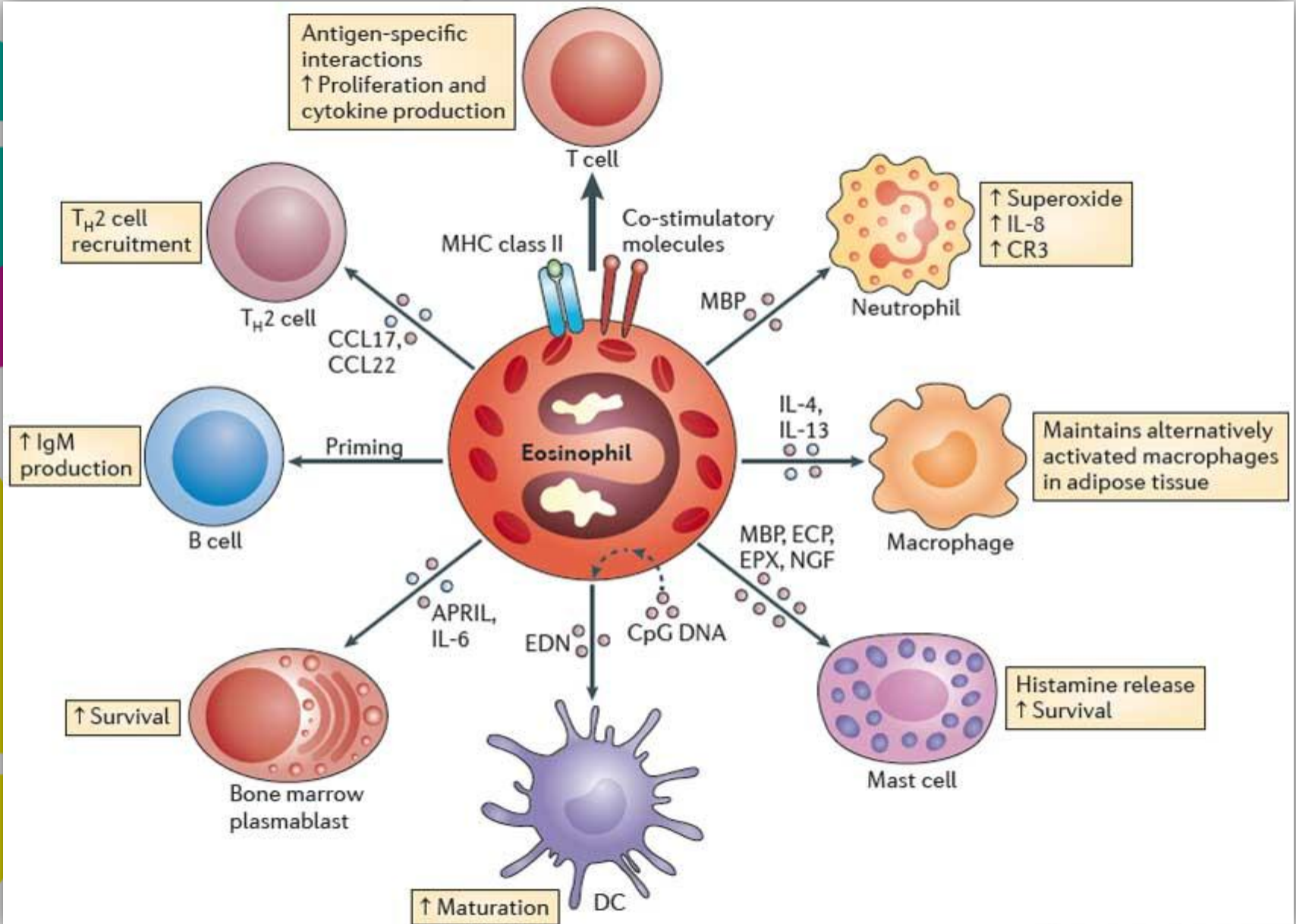


El eosinofilo, la vedette

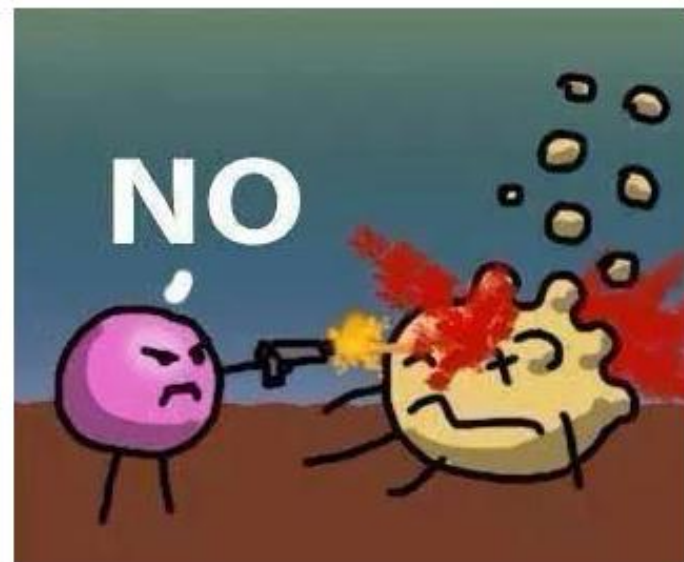


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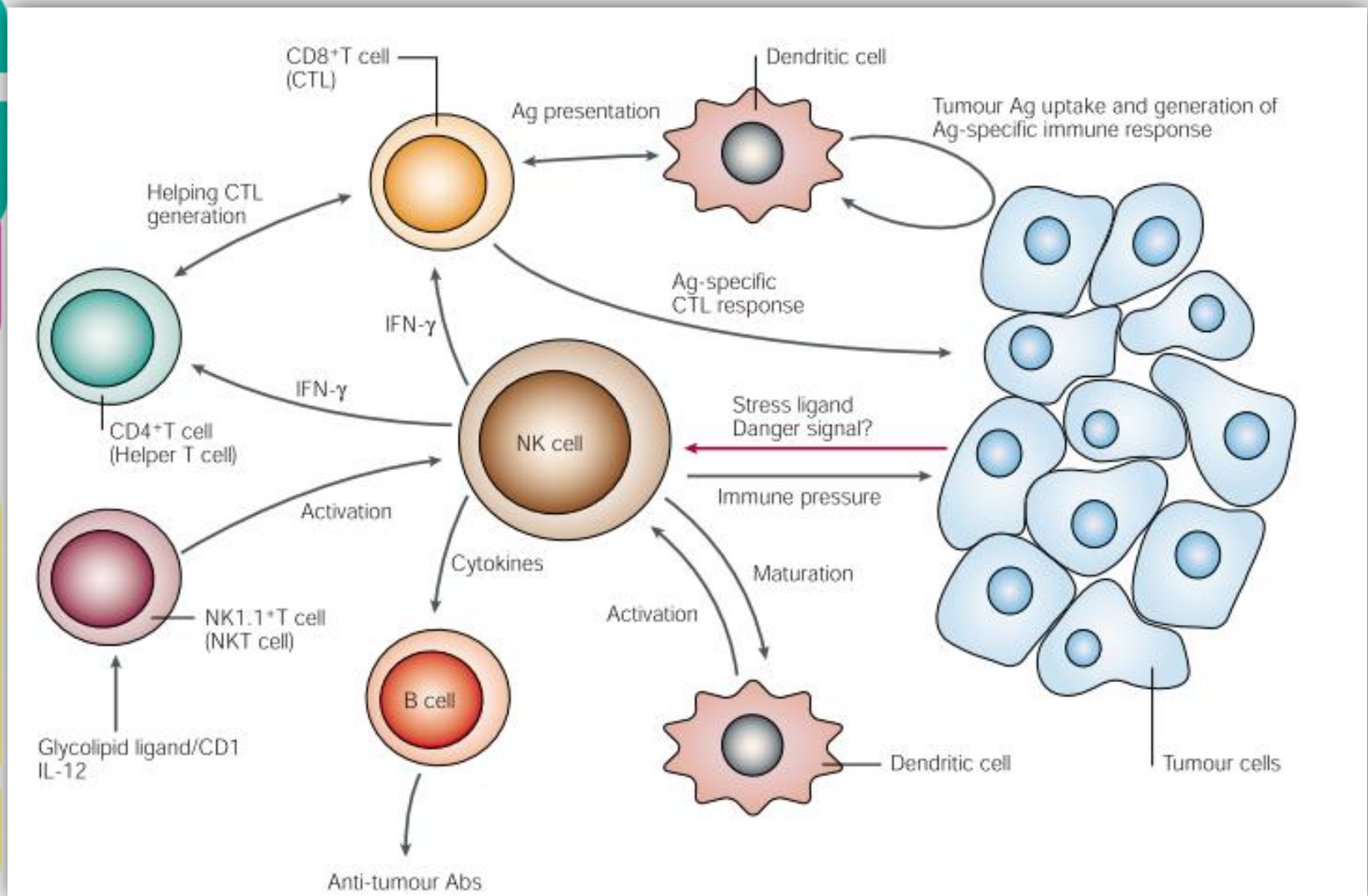
El eosinofilo, la vedette



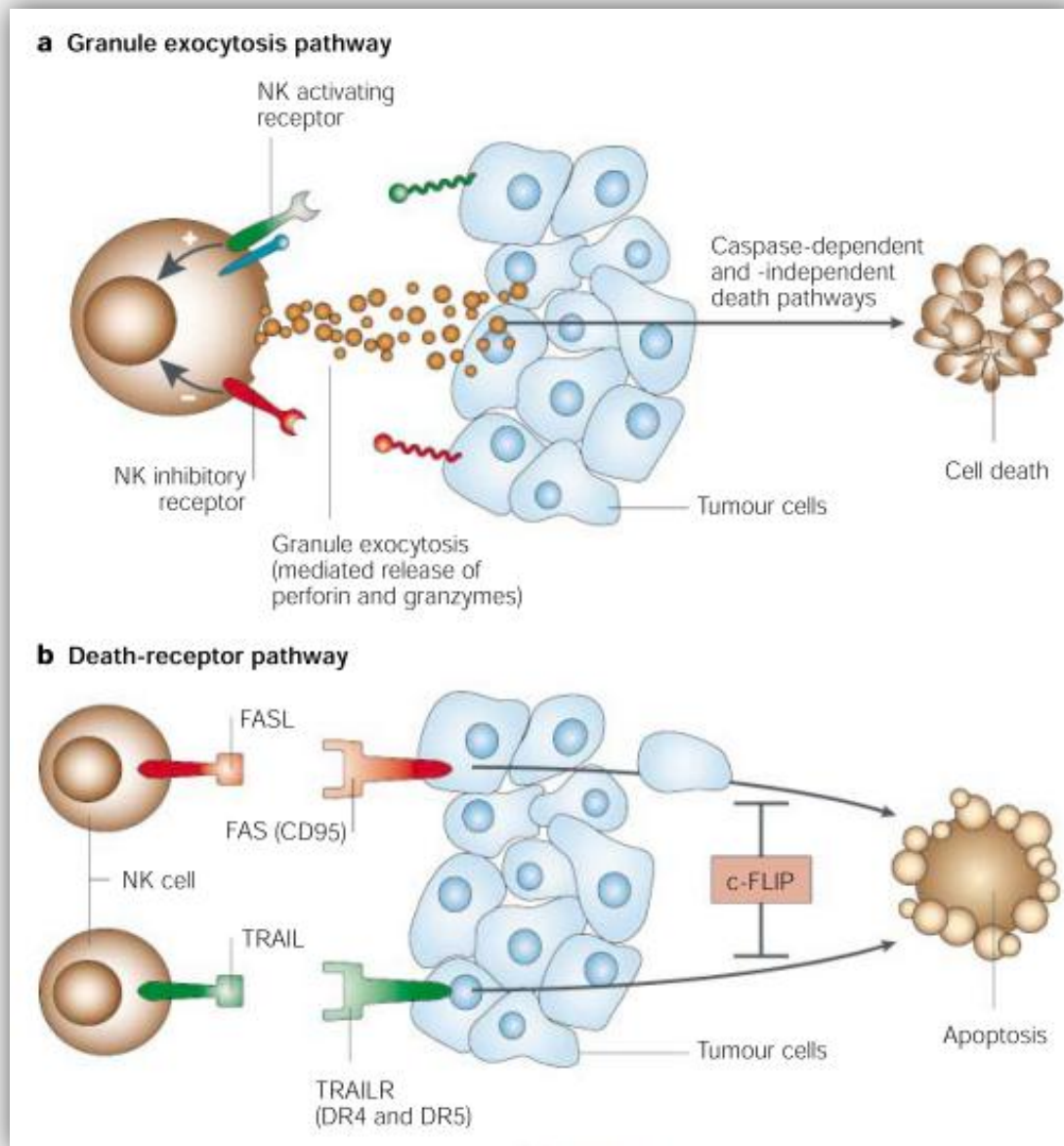
Las asesinas naturales



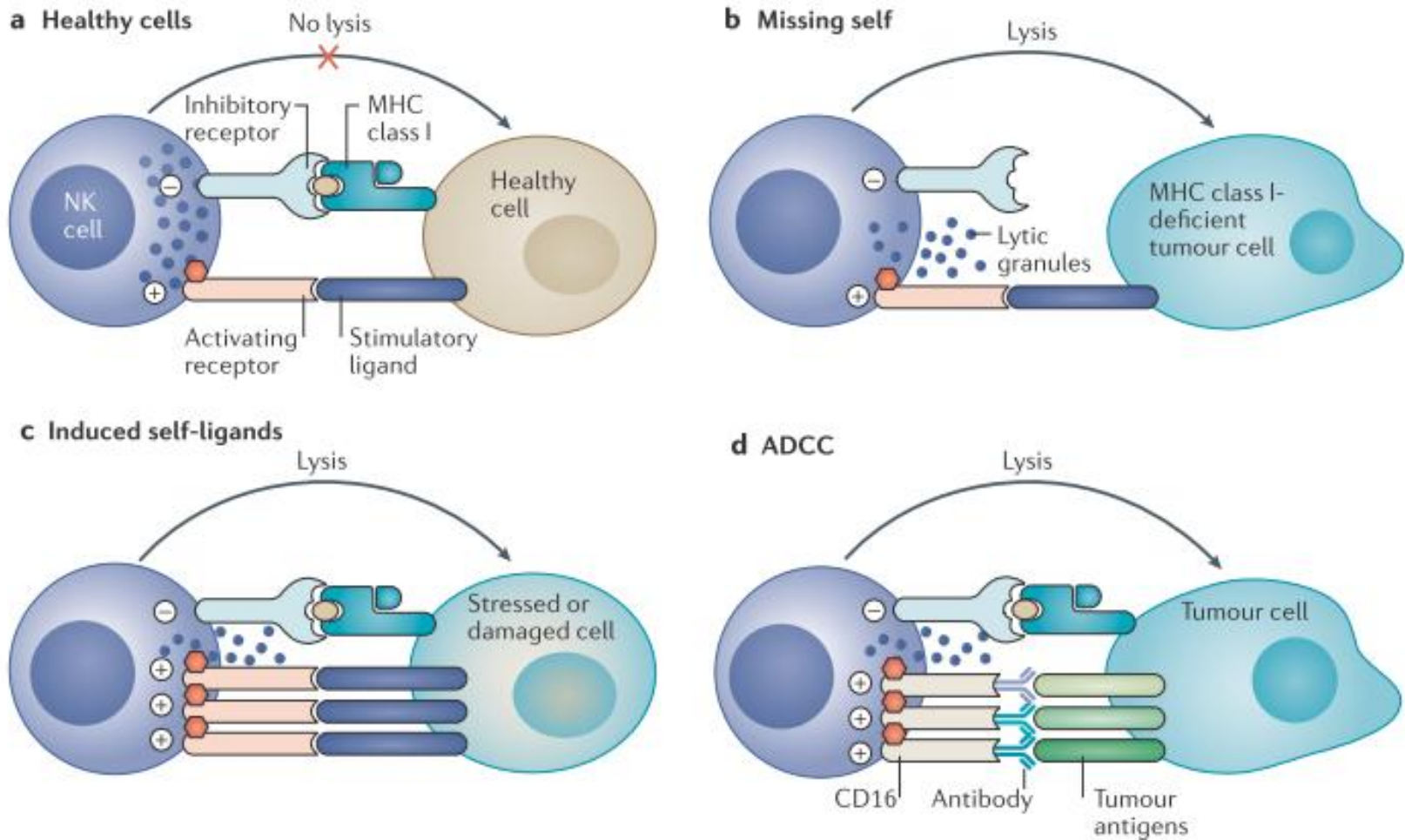
Natural killer



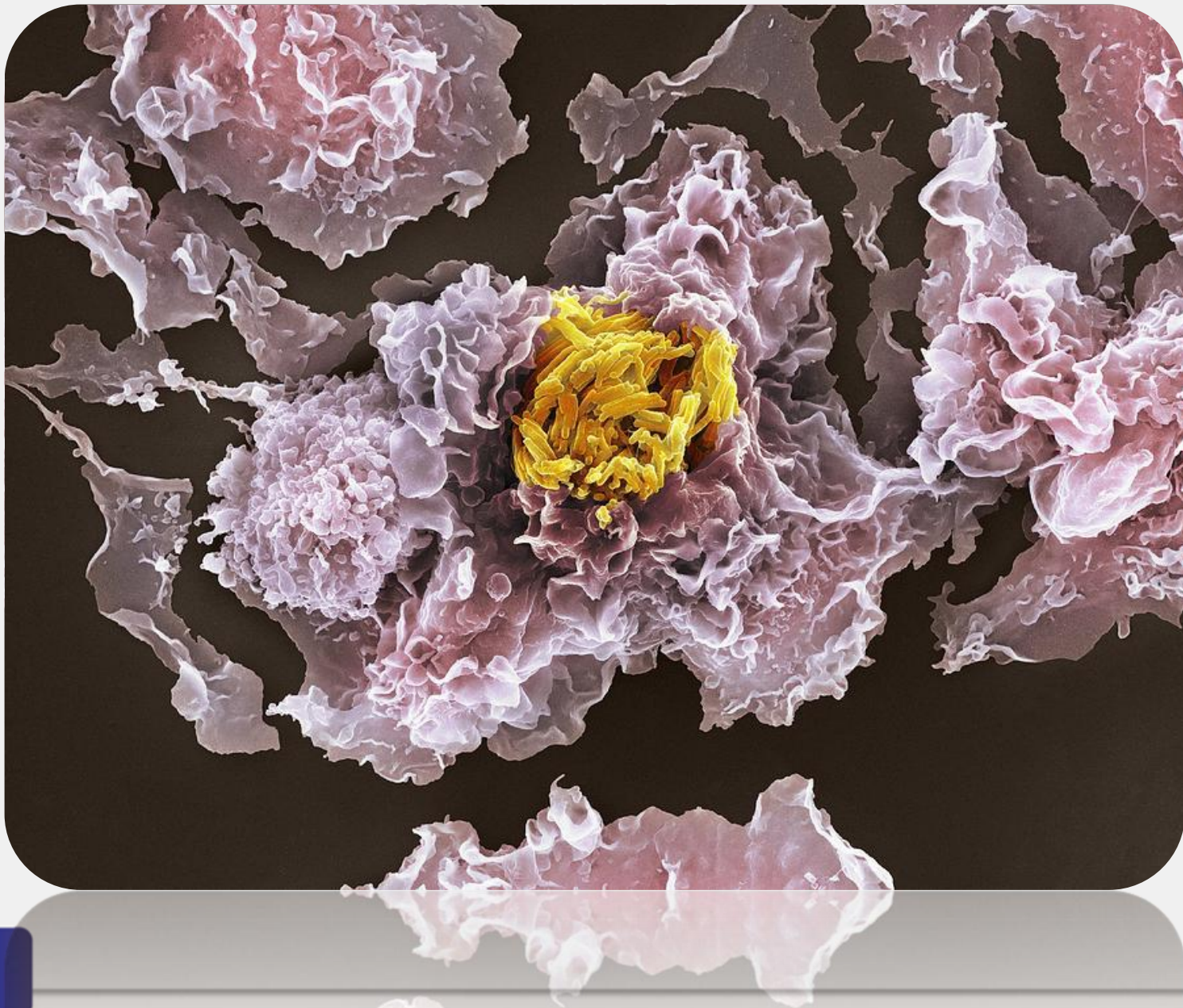
Armas utilizadas



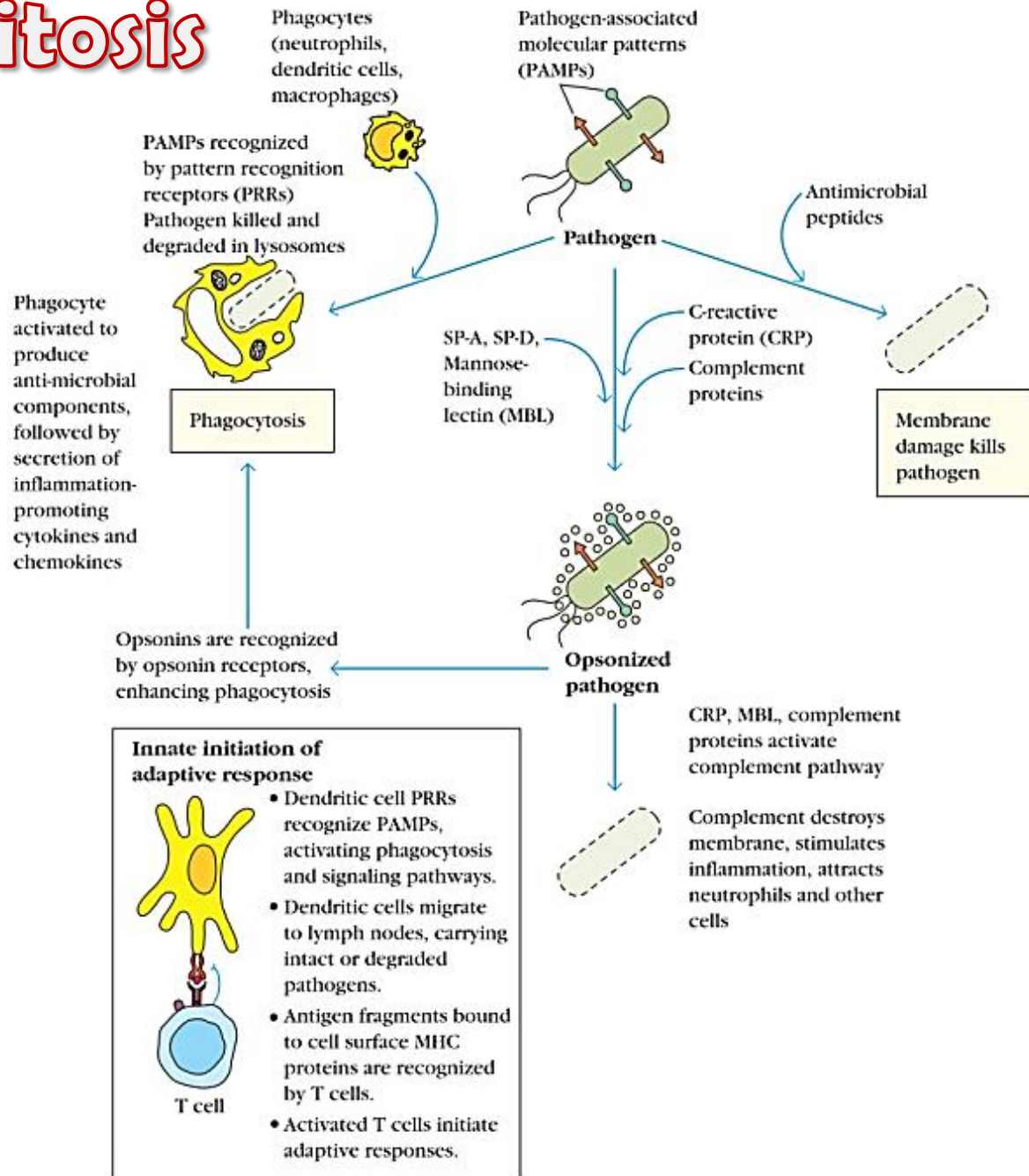
Selección mortal



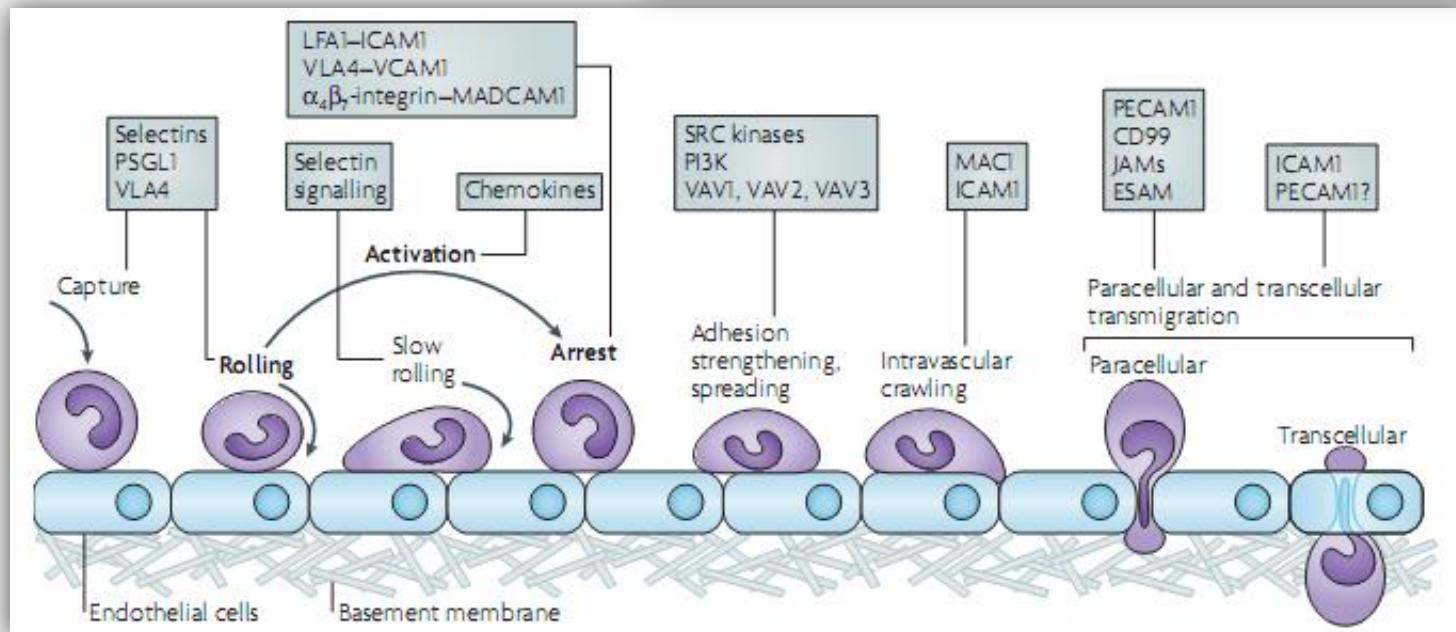
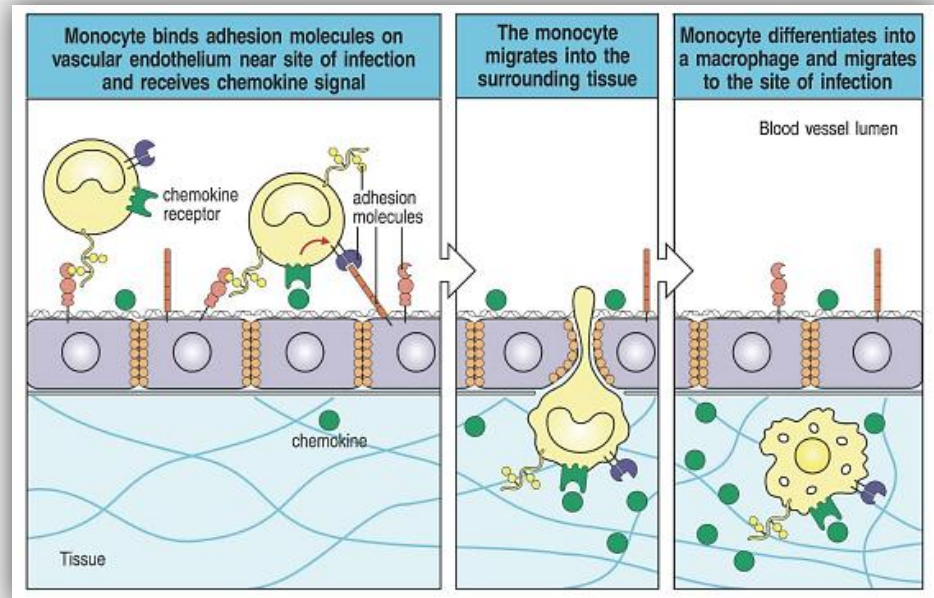
Fagocitos



Fagocytosis



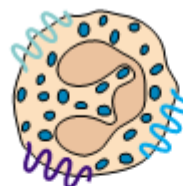
Como Llegan?



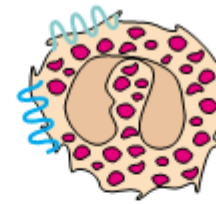
Como llegan?



Neutrophil



Basophil

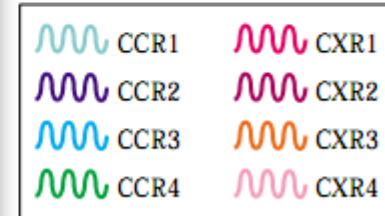


Eosinophil

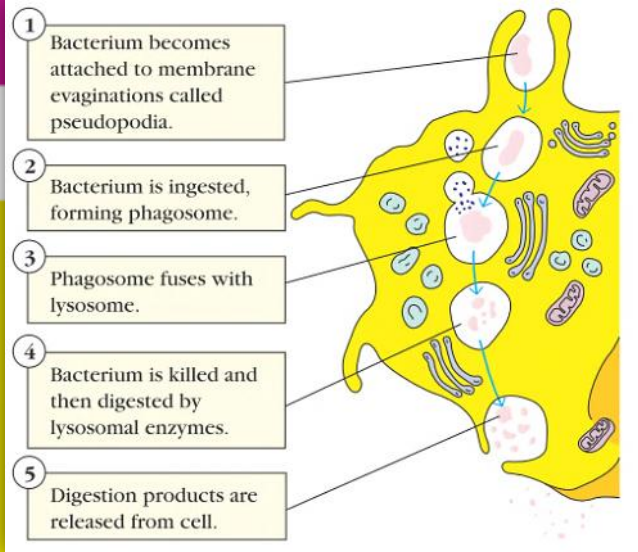


Monocyte

Receptor	Ligand(s)	Function(s)
CCR4	CCL17, CCL22	Migration to normal and inflamed skin Migration to asthmatic airways Migration to sites of inflammation
CCR5	CCL3, CCL4, CCL5, CCL8, CCL11, CCL14, CCL16	Guided encounters with 'helped' DCs in lymph nodes Migration to inflamed tissues Migration to inflamed tissues
CCR6	CCL20	Migration to inflamed tissues
CCR7	CCL19, CCL21	Migration to resting lymph nodes Interstitial motility in lymph nodes Migration to resting lymph nodes
CCR8	CCL1	Migration to normal skin Migration to sites of allergic inflammation
CCR9	CCL25	Migration to lamina propria and GALT
CCR10	CCL27	Migration to normal and inflamed skin
CXCR1	CCL6, CCL8	Migration to inflamed tissues
CXCR3	CCL9-CCL11	Migration to inflamed tissues Migration to inflamed lymph nodes and tissue Migration to inflamed tissues Migration to inflamed tissues
CXCR4	CXCL12	Migration to resting lymph nodes
CXCR5	CXCL13	Migration to T cell-B cell border and GC in lymph nodes
CXCR6	CXCL16	Migration to tissue

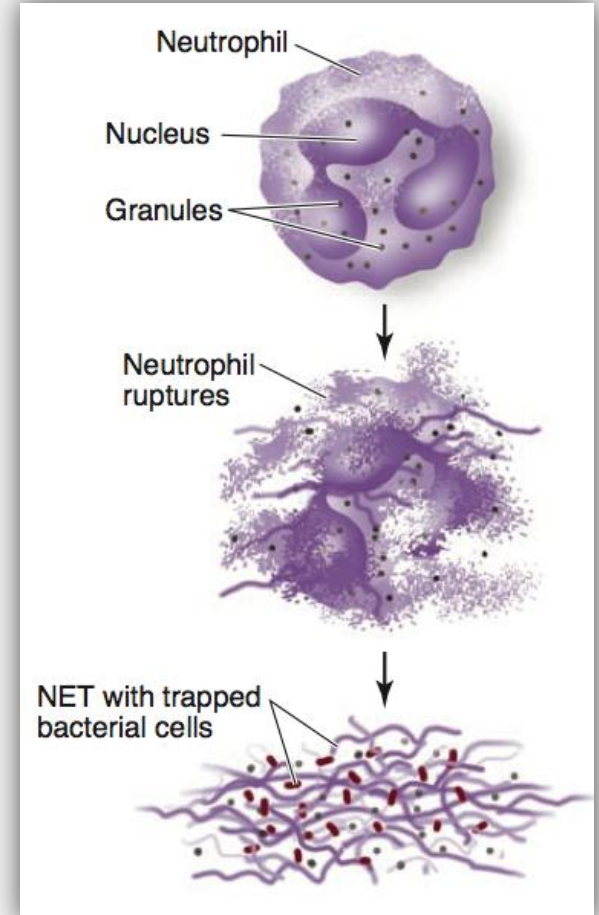
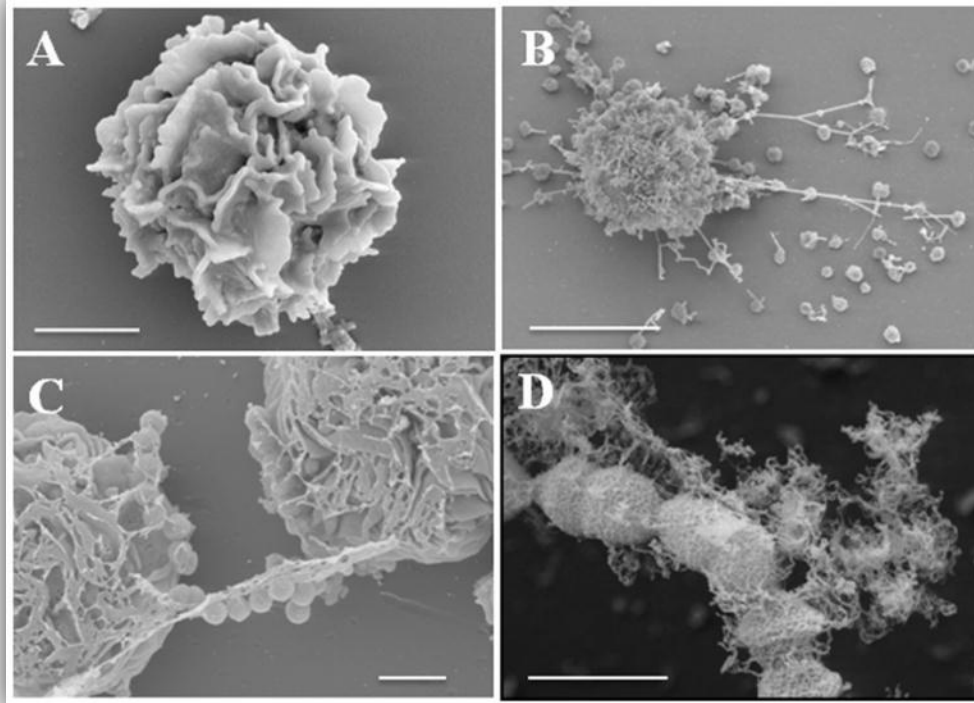


Mecanismos antimicrobianos



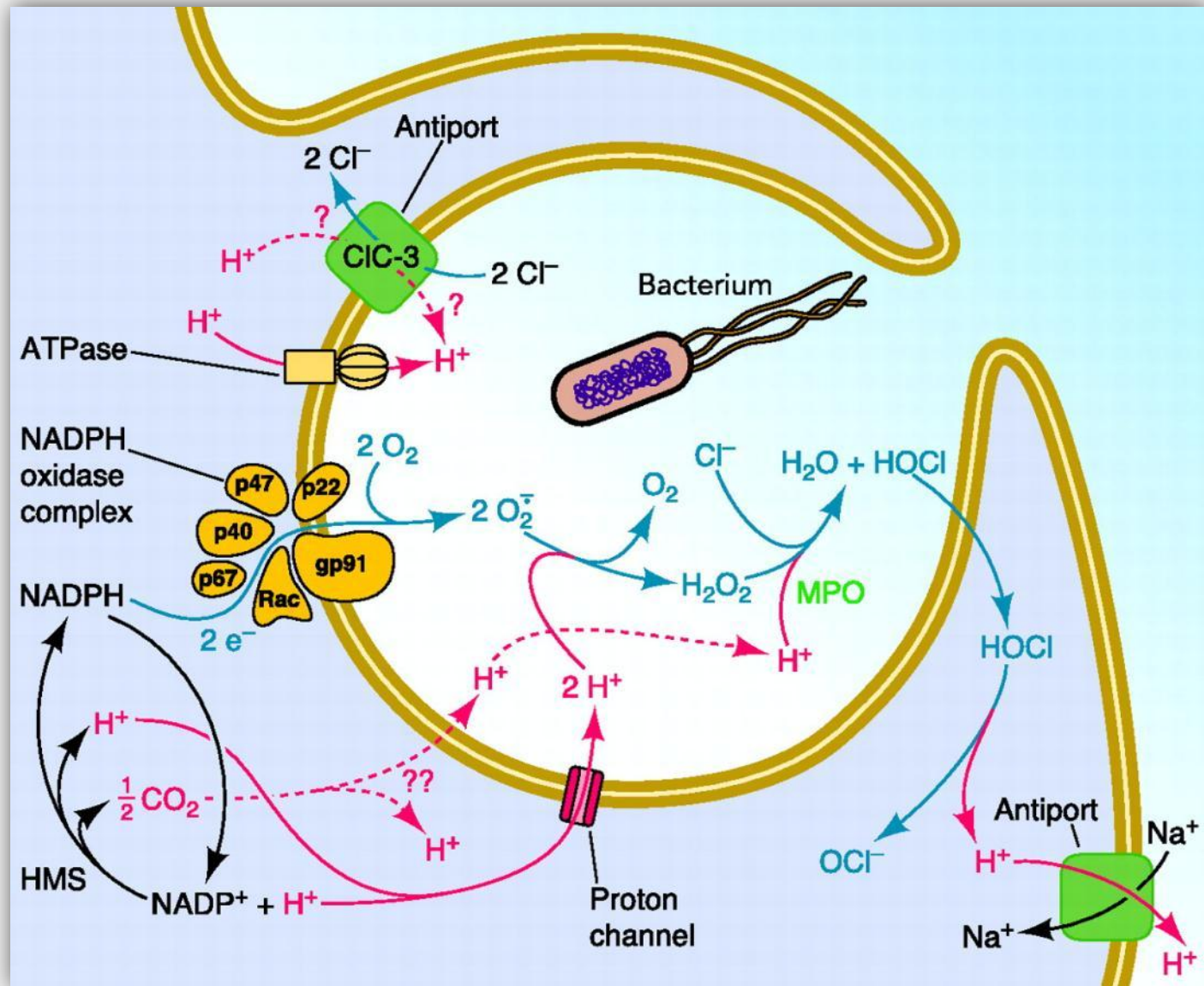
Antimicrobial mechanisms of phagocytes		
Class of mechanism	Macrophage products	Neutrophil products
Acidification	pH~-3.5-4.0, bacteriostatic or bactericidal	
Toxic oxygen-derived products	Superoxide O_2^- , hydrogen peroxide H_2O_2 , singlet oxygen 1O_2 , hydroxyl radical *OH , hypochlorite OCl^-	
Toxic nitrogen oxides	Nitric oxide NO	
Antimicrobial peptides	Cathelicidin, macrophage elastase-derived peptide	α -Defensins (HNP1-4), β -defensin HBD4, cathelicidin, azurocidin, bacterial permeability inducing protein (BPI), lactoferrin
Enzymes	Lysozyme: digests cell walls of some Gram-positive bacteria Acid hydrolases (e.g. elastase and other proteases): break down ingested microbes	
Competitors		Lactoferrin (sequesters Fe^{2+}), vitamin B_{12} -binding protein

NET = NOS EXPLOTAMOS TODOSSSSSS



- NET: Neutrophil extracellular traps

Estallido respiratorio

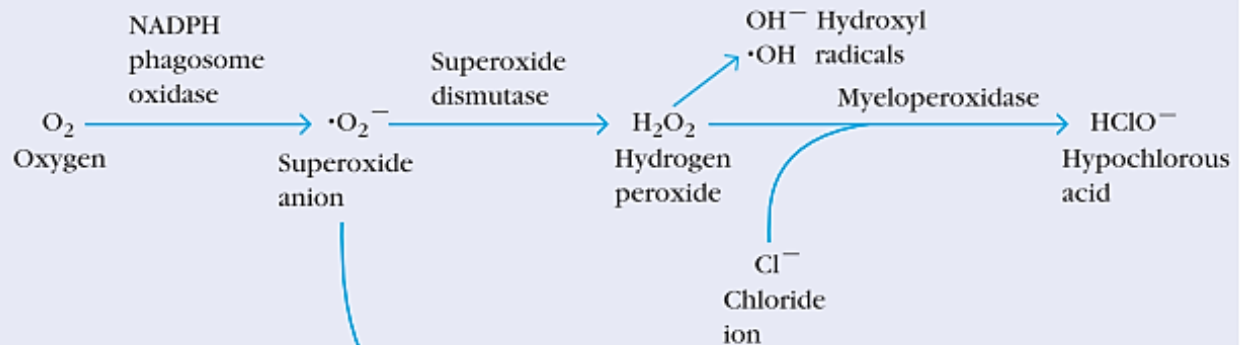


Radicales oxidativos

Antimicrobial species generated from oxygen and nitrogen

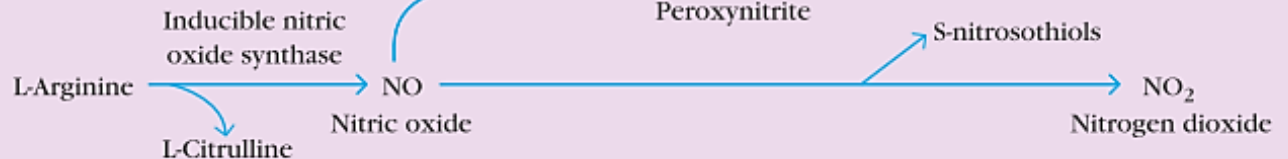
Reactive oxygen species (ROS)

- $\cdot\text{O}_2^-$ (superoxide anion)
- $\text{OH}\cdot$ (hydroxyl radical)
- H_2O_2 (hydrogen peroxide)
- HClO (hypochlorous acid)



Reactive nitrogen species (RNS)

- NO (nitric oxide)
- NO_2 (nitrogen dioxide)
- ONOO^- (peroxynitrite)



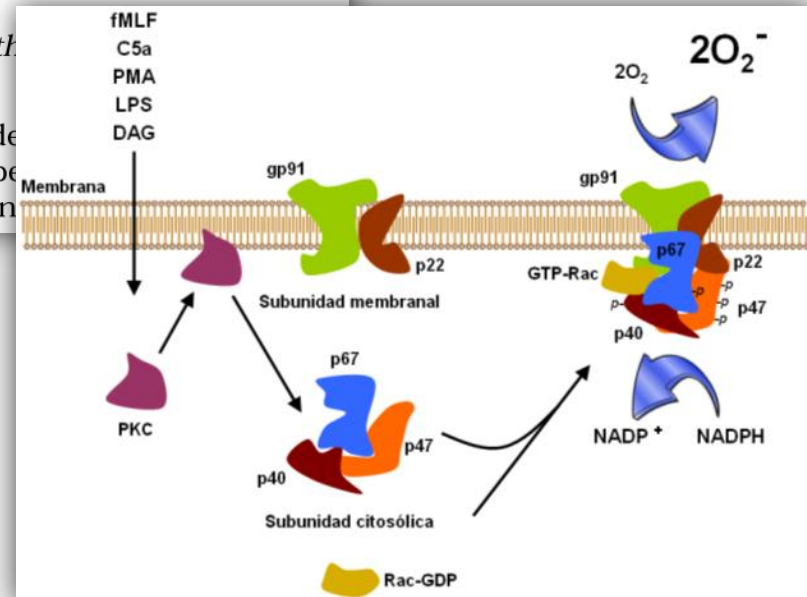
Enfermedad Granulomatosa Crónica

Invest Clin 40(4): 277-300, 1999

El complejo NADPH-oxidasa en la enfermedad granulomatosa crónica: Descripción preliminar de un foco en Mérida-Venezuela.

Siham Salmen¹, Lisbeth Berrueta¹, Paul Heyworth¹, Manuel Hernández¹ y José Muñoz¹.

¹Instituto de Inmunología Clínica, Universidad de Venezuela y ²Department of Molecular and Experimental Medicine, The Scripps Research Institute, La Jolla, California



INFECCIONES Y CONDICIONES CRÓNICAS QUE SE PRESENTAN EN LA ENFERMEDAD GRANULOMATOSA CRÓNICA

INFECCIONES	% DE EPISODIOS	MICROORGANISMOS INVOLUCRADOS	% DE AISLADOS	CONDICIONES CRÓNICAS ASOCIADAS	% DE CASOS
Neumonía	70-80	<i>Staphylococcus aureus</i>	30-50	Linfadenopatía	98
Linfadenitis	60-80	<i>Aspergillus sp</i>	10-20	Hipergammaglobulinemia	60-90
Infecciones cutáneas/impétigo	60-70	<i>Escherichia coli</i>	5-10	Hepatomegalia	50-90
Hepatitis /absceso perihepático	30-40	<i>Klebsiella sp</i>	5-10	Esplenomegalia	60-80
Osteomielitis	20-30	<i>Salmonella sp</i>	5-10	Anemia crónica	Común
Abscesos perirectal/fistulas	15-30	<i>Pseudomona cepacia y aeruginosa</i>	5-10	Bajo peso	70
Septicemia	10-20	<i>Serratia marcescens</i>	5-10	Diarrea crónica	20-60
Otitis media	20	<i>Staphylococcus epidermidis</i>	5	Baja estatura	50
Conjuntivitis	15	<i>Streptococcus sp</i>	4	Gingivitis	50
Infecciones entéricas	10	<i>Enterobacter sp</i>	3	Dermatitis	35
Infección del tracto urinario/pielonefritis	5-15	<i>Proteus sp</i>	3	Hidronefrosis	10-25
Sinusitis	<10	<i>Candida albicans</i>	3	Estomatitis ulcerativa	5-15
Renal/abscesos periférico	<10	<i>Nocardia sp</i>	2	Fibrosis pulmonar	<10
Absceso cerebral	<5	<i>Haemophilus influenzae</i>	1	Esofagitis	<10
Pericarditis	<5	<i>Pneumocystis carinii</i>	<1	Estrechez gástrica antral	<10
Meningitis	<5	<i>Mycobacterium fortuitum</i>	<1	Ileocolitis granulomatosa	<10
		<i>Chromobacterium violaceum</i>	<1	Corioretinitis	<10
		<i>Francisella philomiragia</i>	<1	Cistitis granulomatosa	<10
		<i>Torulopsis glabrata</i>	<1	Glomerulonefritis	<10
				Lupus eritematoso discoide	<10

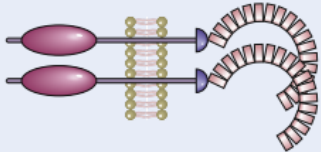




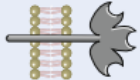


Recuerdan lo de la diferencia?

	Innate Immunity	Adaptive Immunity
Specificity For structures shared by classes of microbes (pathogen-associated molecular patterns)	For structural detail of microbial molecules (antigens); may recognize nonmicrobial antigens	
Different microbes Toll-like receptor	Different microbes Distinct antibody molecules	
Receptors Encoded in germline; limited diversity (pattern recognition receptors)	Encoded by genes produced by somatic recombination of gene segments; greater diversity	
Toll-like receptor Formyl peptide receptor Mannose receptor Scavenger receptor	Ig TCR	
Distribution of receptors	Nonclonal: identical receptors on all cells of the same lineage	Clonal: clones of lymphocytes with distinct specificities express different receptors
Discrimination of self and non-self	Yes; healthy host cells are not recognized or they may express molecules that prevent innate immune reactions	Yes; based on elimination or inactivation of self-reactive lymphocytes; may be imperfect (giving rise to autoimmunity)



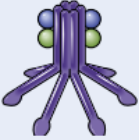

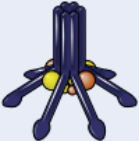
Como reconocen?

TABLE 4-3 Pattern Recognition Molecules of the Innate Immune System

Pattern Recognition Receptors	Location	Specific Examples	PAMP/DAMP Ligands
Cell-Associated			
Toll-like receptors (TLRs) 	Plasma membrane and endosomal membranes of dendritic cells, phagocytes, B cells, endothelial cells, and many other cell types	TLRs 1-9	Various microbial molecules including bacterial LPS and peptidoglycans, viral nucleic acids
NOD-like receptors (NLRs) 	Cytosol of phagocytes, epithelial cells, and other cells	NOD1/2 NLRP family (inflammasomes)	Bacterial cell wall peptidoglycans Intracellular crystals (urate, silica); changes in cytosolic ATP and ion concentrations; lysosomal damage
RIG-like receptors (RLRs) 	Cytosol of phagocytes and other cells	RIG-1, MDA-5	Viral RNA
Cytosolic DNA sensors (CDSs) 	Cytosol of many cell types	AIM2; STING-associated CDSs	Bacterial and viral DNA
C-type lectin-like receptors (CLRs) 	Plasma membranes of phagocytes	Mannose receptor Dectin	Microbial surface carbohydrates with terminal mannose and fructose Glucans present in fungal cell walls
Scavenger receptors 	Plasma membranes of phagocytes	CD36	Microbial diacylglycerides

Como reconocen?

TABLE 4-3 Pattern Recognition Molecules of the Innate Immune System

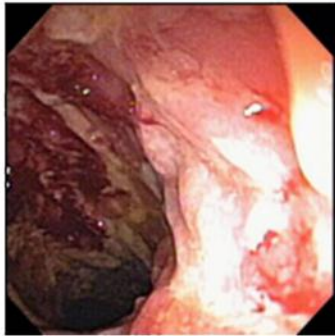
Pattern Recognition Receptors	Location	Specific Examples	PAMP/DAMP Ligands
Cell-Associated			
<i>N</i> -Formyl met-leu-phe receptors 	Plasma membranes of phagocytes	FPR and FPRL1	Peptides containing <i>N</i> -formylmethionyl residues
Soluble			
Pentraxins 	Plasma	C-reactive protein	Microbial phosphorylcholine and phosphatidylethanolamine
Collectins 	Plasma	Mannose-binding lectin	Carbohydrates with terminal mannose and fructose
	Alveoli	Surfactant proteins SP-A and SP-D	Various microbial structures
Ficolins 	Plasma	Ficolin	<i>N</i> -Acetylglucosamine and lipoteichoic acid components of the cell walls of gram-positive bacteria
Complement 	Plasma	Various complement proteins	Microbial surfaces

Cruciales en la homeostasis



Genetic associations of TLR and NLR to inflammatory disorders.

TLR/NLR	Inflammatory disorder
TLR2	Asthma, acute rheumatic fever, Lepromatous leprosy
TLR4	Asthma, Crohn's disease, ulcerative colitis
TLR10	Asthma, atopic eczema, increased serum IgE
NOD1	Asthma, atopic eczema, increased serum IgE, IBD (Crohn's disease and Ulcerative colitis)
NOD2	Atopic dermatitis, Blau syndrome, Crohn's disease, early-onset sarcoidosis, graft-versus-host disease (GVHD)
NALP1	Vitiligo, autoimmune thyroid disease, Addison's disease, RA, psoriasis, SLE
NALP3	Hereditary periodic fever syndromes [familial Mediterranean fever (FMF), chronic neurogenic cutaneous and articular syndrome (CINCA), Muckle-Wells syndrome (MWS), familial cold autoinflammatory syndrome (FCAS), and pyogenic sterile arthritis with pyoderma gangrenosum and acne (PAPA)]



Crohn's disease of the ileum showing typical cobblestoning and ulcerations of the mucosa.



Ulcerative colitis of the transverse colon with granularity and friability of the mucosa. Note there are not deep ulcerations.

Peligro? Daño?

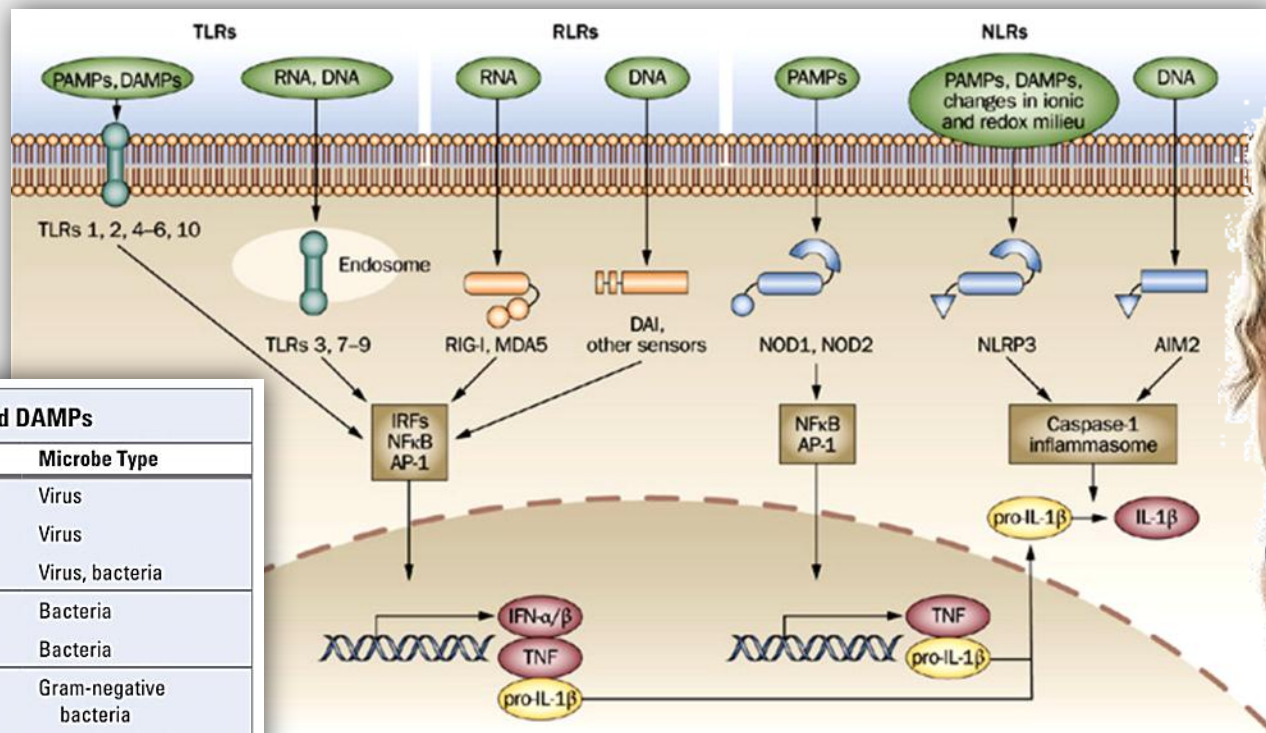


TABLE 4-2 Examples of PAMPs and DAMPs

Pathogen-Associated Molecular Patterns		Microbe Type
Nucleic acids	ssRNA	Virus
	dsRNA	Virus
	CpG	Virus, bacteria
Proteins	Pilin	Bacteria
	Flagellin	Bacteria
Cell wall lipids	LPS	Gram-negative bacteria
	Lipoteichoic acid	Gram-positive bacteria
Carbohydrates	Mannan	Fungi, bacteria
	Glucans	Fungi
Damage-Associated Molecular Patterns		
Stress-induced proteins	HSPs	
Crystals	Monosodium urate	
Nuclear proteins	HMGB1	

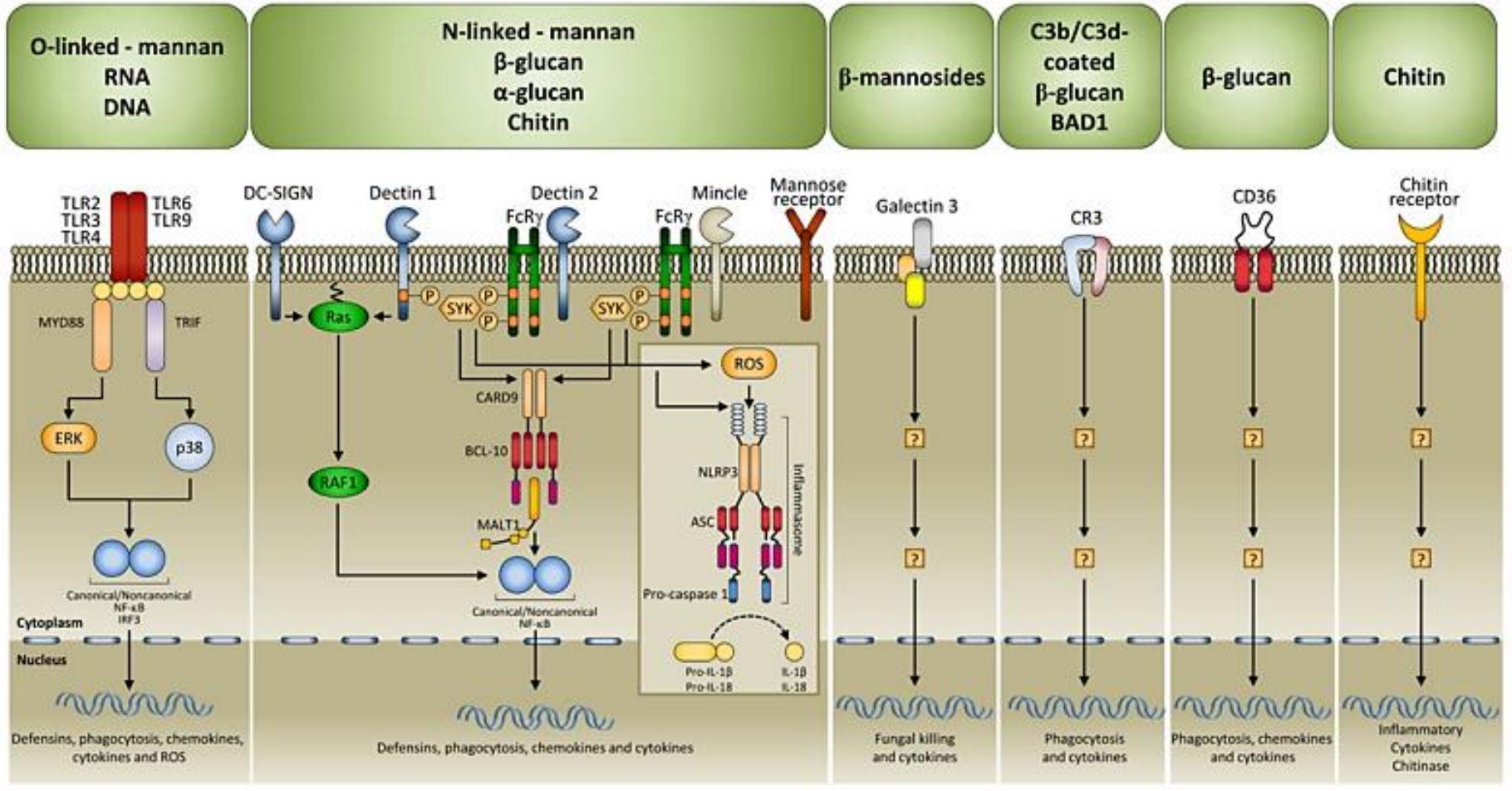
CpG, cytosine-guanine-rich oligonucleotide; *dsRNA*, double-stranded RNA; *HMGB1*, high-mobility group box 1; *HSP*, heat shock protein; *LPS*, lipopolysaccharide; *ssRNA*, single-stranded RNA.

- TLRs, RLRs & NLRs vs PAMPs, DAMPs

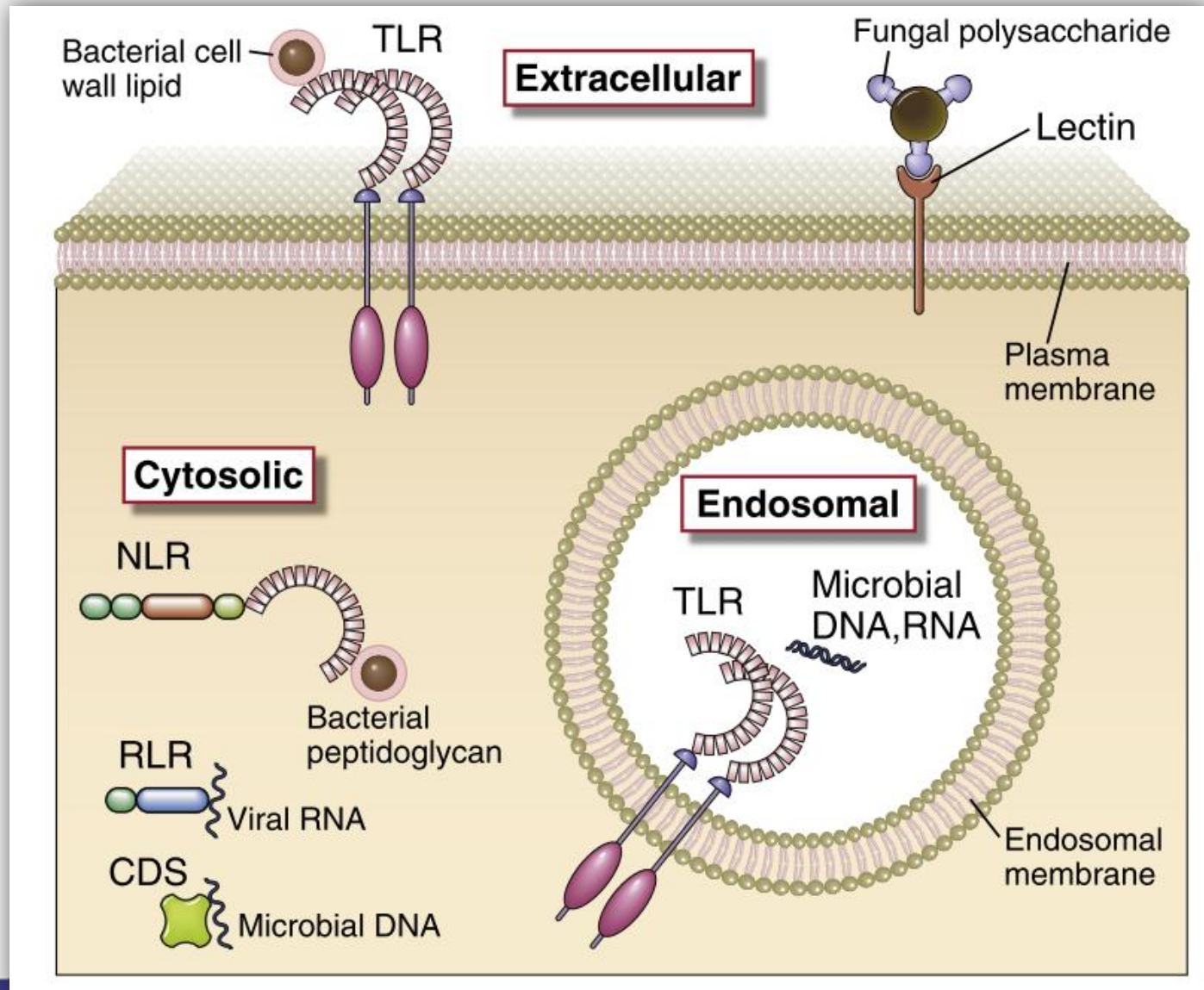


Sensores de la inmunidad innata

PAMP's Recognition



Distribución subcelular

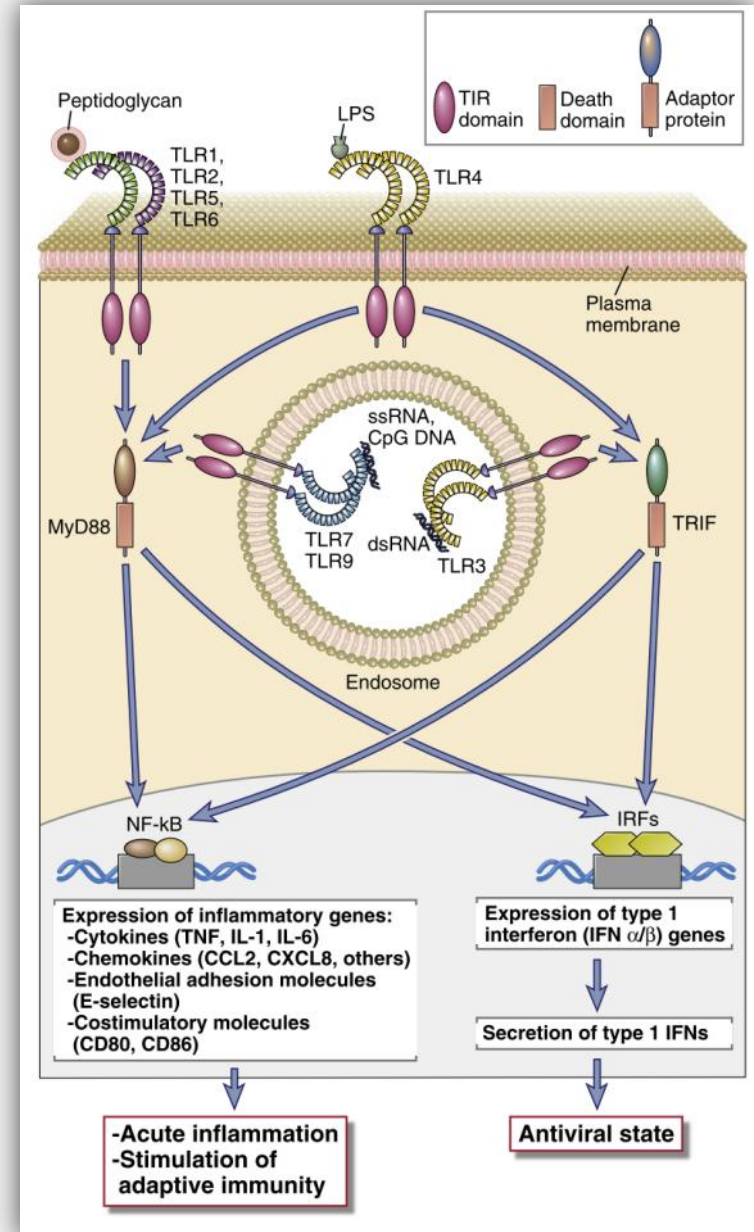
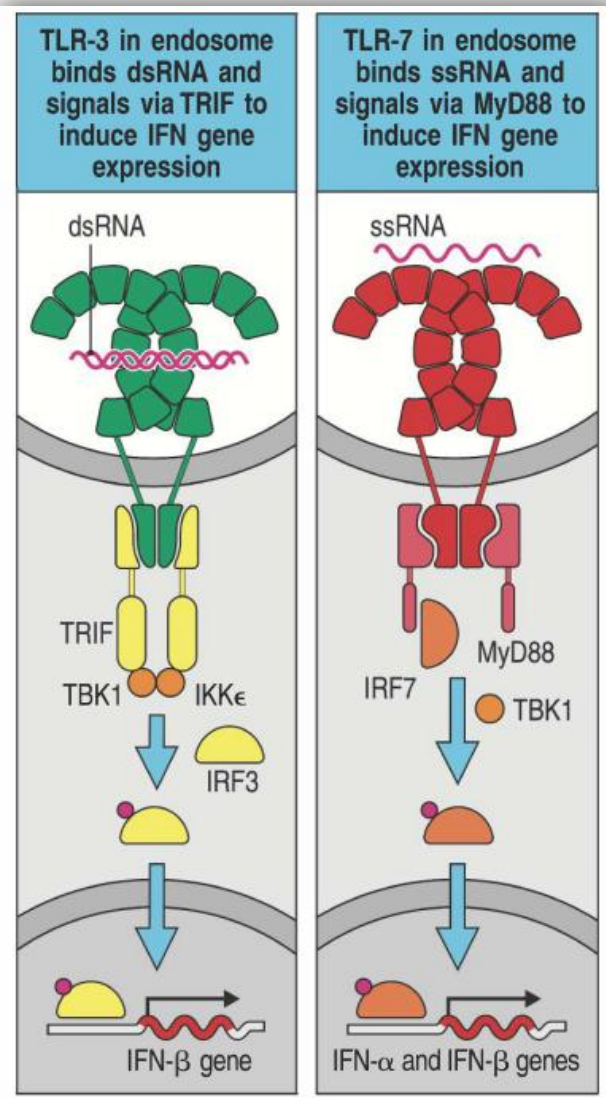


Ejemplos de Toll like receptors

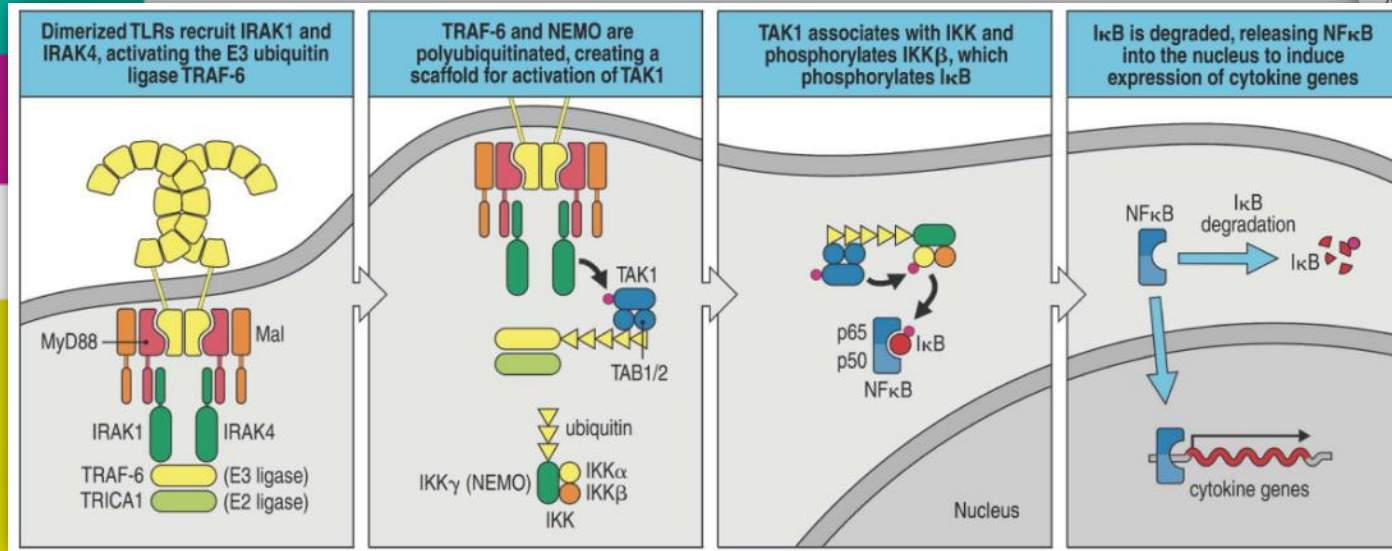
Innate immune recognition by mammalian Toll-like receptors

Toll-like receptor	Ligand	Cellular distribution
TLR-1:TLR-2 heterodimer	Lipomannans (mycobacteria) Lipoproteins (diacyl lipopeptides; triacyl lipopeptides) Lipoteichoic acids (Gram-positive bacteria) Cell-wall β -glucans (bacteria and fungi) Zymosan (fungi)	Monocytes, dendritic cells, mast cells, eosinophils, basophils
TLR-2:TLR-6 heterodimer		
TLR-3	Double-stranded RNA (viruses)	NK cells
TLR-4 (plus MD-2 and CD14)	LPS (Gram-negative bacteria) Lipoteichoic acids (Gram-positive bacteria)	Macrophages, dendritic cells, mast cells, eosinophils
TLR-5	Flagellin (bacteria)	Intestinal epithelium
TLR-7	Single-stranded RNA (viruses)	Plasmacytoid dendritic cells, NK cells, eosinophils, B cells
TLR-8	Single-stranded RNA (viruses)	NK cells
TLR-9	DNA with unmethylated CpG (bacteria and herpesviruses)	Plasmacytoid dendritic cells, eosinophils, B cells, basophils
TLR-10	Unknown	Plasmacytoid dendritic cells, eosinophils, B cells, basophils
TLR-11 (mouse only)	Profilin and profilin-like proteins (<i>Toxoplasma gondii</i> , uropathogenic bacteria)	Macrophages, dendritic cells, liver, kidney, and bladder epithelial cells

Diferentes vías de señalización



Toll like receptors TLR

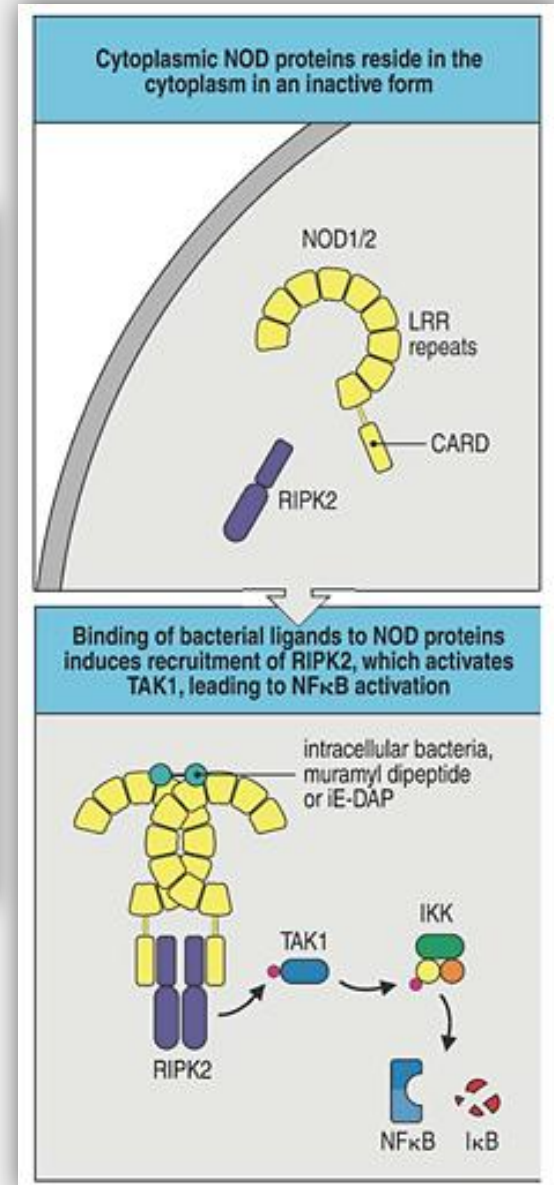


TLR2 Polymorphisms and susceptibility to diseases	
SNP	Diseases
Arg753Gln	Gram-positive septic shock
Arg753Gln	Lyme disease
Arg753Gln	<i>S. aureus</i>
Arg753Gln	Febrile infections
Arg753Gln	Tuberculosis
Arg753Gln	Cytomegalovirus disease
Arg753Gln	Viral infection
Arg753Gln	Fungal colonization
Arg753Gln	Fungal infection
97C	TB Meningitis
ron 2	Tuberculosis
microsatellite	
Arg753Gln	Rheumatic fever
Arg753Gln	Rheumatic heart disease
Arg753Gln	Chronic periodontitis
Arg753Gln	Generalized aggressive periodontitis
Arg753Gln	Chronic periodontitis
Arg753Gln	Atopic dermatitis
Arg753Gln	Crohn's disease

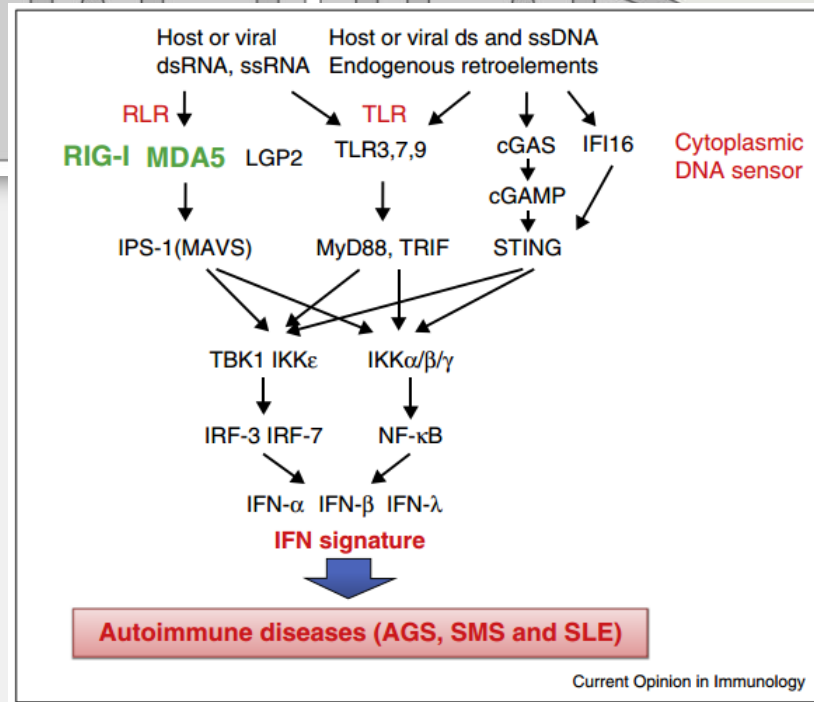
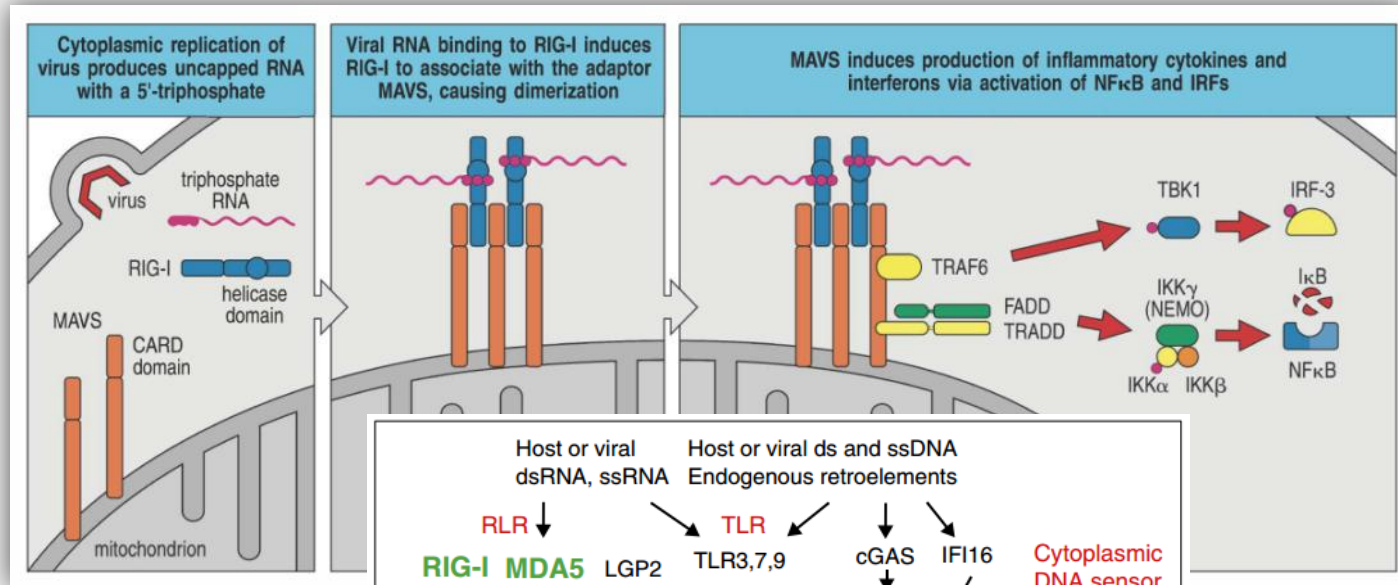


NOD-like receptors

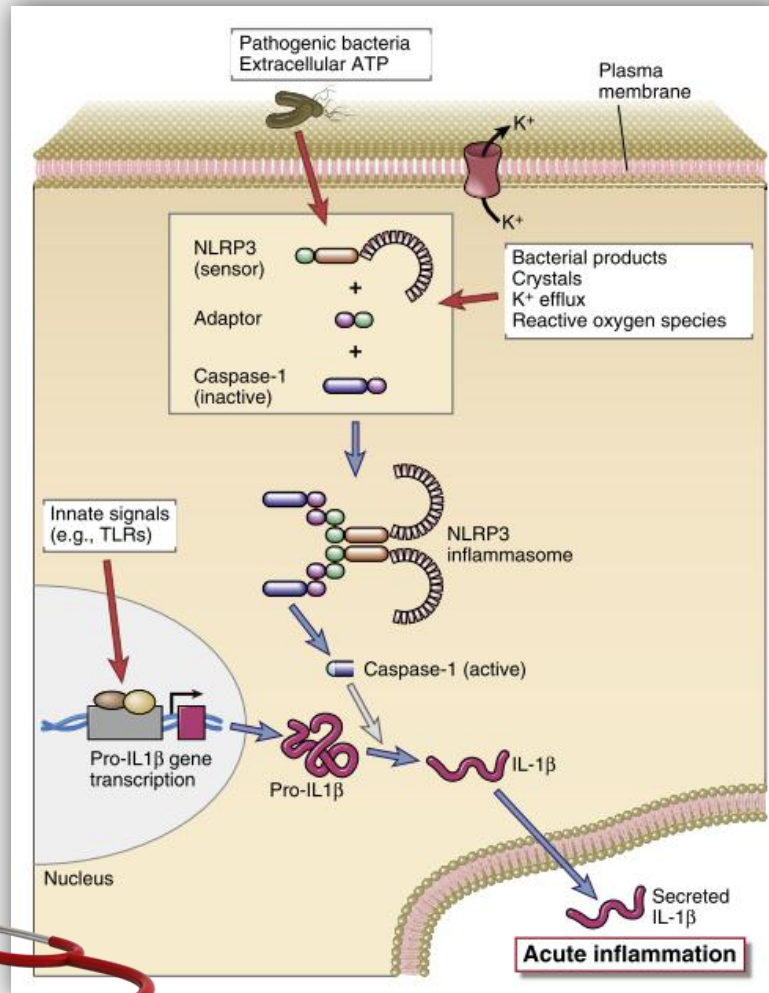
Family	Protein	Polymorphism	Associated diseases
NLRC	NOD2	<i>Mutations in the LRR</i> e.g. 1007fs, R702W, G908R	Crohn's disease
		<i>Mutations in the NOD</i> e.g. L469F, R334Q, R334W	Blau syndrome Asthma Atopic eczema, atopic dermatitis Arthritis Sarcoidosis Prostate and endometrial cancer Gastric lymphoma Leprosy
	NLRC4		Susceptibility to bacterial infections



RIG-I like receptors

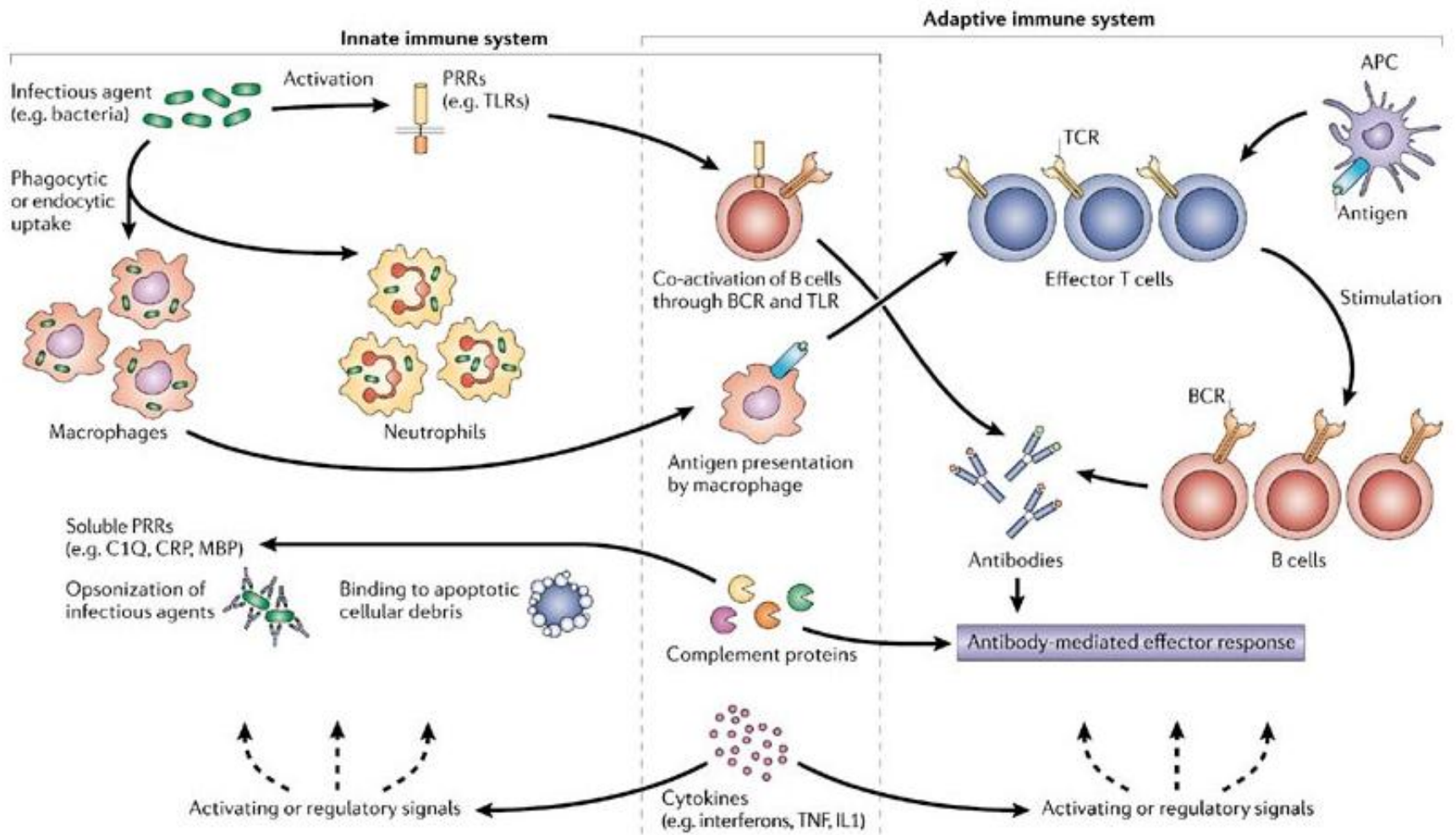


El inflammasoma



Disease	Clinical features	Gene mutated
Familial cold autoinflammatory syndrome (FCAS)	Fever, arthralgia, cold-induced urticaria	NALP3
Muckle-Wells syndrome (MWS)	Fever, arthralgia, urticaria, sensorineural deafness, amyloidosis	NALP3
Chronic infantile neurological cutaneous and articular syndrome (CINCA, NOMID)	Fever, severe arthralgia, urticaria, neurological problems, severe amyloidosis	NALP3
Familial Mediterranean fever (FMF)	Fever, peritonitis, pleuritis, amyloidosis	Pyrin
Pyogenic arthritis, pyoderma gangrenosum, and acne syndrome (PAPA)	Pyogenic sterile arthritis	PSTPIP1
Hyperimmunoglobulin D syndrome (HIDS)	Arthralgia, abdominal pain, lymphadenopathy	Mevalonate kinase
Tumor necrosis factor receptor-1-associated syndrome (TRAPS)	Fever, abdominal pain, skin lesions	TNF-R1
Systemic juvenile idiopathic arthritis (SOJIA)	Chronic joint inflammation	
Adult-onset Still's disease (AOSD)	Arthralgia, fever	
Behcet's disease	Arthralgia, uveitis, ulcers	
Schnitzler's syndrome	Urticaria, fever arthralgia	
Gout	Metabolic arthritis, pain	
Pseudogout	Arthritis	
Contact dermatitis	Urticaria	
Fever syndrome	Fever	NALP12
Hydatidiform mole	Hydatid mole	NALP7
Vitiligo	Skin depigmentation, automimmunity	NALP1

Bidireccionalidad



¡Pregunten Ahora o Callen Para Siempre!



Guillermo Teran-Angel
guillermondi@gmail.com
<http://guillermo.vv.si>



**¡Gracias por la
atención!**